multiple liver lesions compatible with hepatocellular carcinoma. The subject was treated with ursodeoxycholic and prednisolone. On 11 Mar 2015 (Day 106), the severity of hepatic function abnormal improved to Grade 2. Laboratory tests showed ALT 154 U/L (NR: 8 – 42), AST 71 U/L (NR: 13 – 33), and total bilirubin 18.81 umol/L. The subject was treated with prednisolone. On the same day (Day 106), study drug was resumed at a reduced frequency of 400 mg every other day due to abnormal hepatic function. On 24 Jun 2015 (Day 211), the subject recovered from abnormal hepatic function with AST 35 U/L (NR: 13 – 33) and ALT 17 U/L (NR: 8 – 42). The Investigator considered abnormal hepatic function serious (important medical event) and possibly related to the study drug.

On 01 Apr 2015 (Day 127), tumor response assessment showed disease progression. On 08 Apr 2015 (Day 134), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on the same day (Day 134).

On 11 May 2016 (Day 533, 399 days after the last dose), the subject died due to disease progression.

Subject Number	12081004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01233-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Abdominal pain
AE(s) Leading to Discontinuation	Abdominal pain

A 79-year-old Japanese female was diagnosed with hepatocellular carcinoma on 31 Jul 2006. Significant medical history included chronic gastritis, chronic hepatitis C, esophageal varices, hypertension, insomnia, hepatic cirrhosis, osteoarthritis, osteoporosis, and spondylolisthesis. Previous anticancer therapies included radiofrequency ablation (6x), transcatheter arterial chemoembolization (10x) and radiotherapy to T12 vertebrae. Prior and concomitant medications included alendronic acid, carbohydrates w/potassium chloride/sodium lactate, cefmetazole, fentanyl, heparin, l-carbocysteine, lactobacillus casei, losartan, loxoprofen, oxycodone, pa (salicylamide acetaminophen anhydrous caffeine promethazine methylenedisalicylate), paracetamol, prochlorperazine, rabeprazole, rebamipide, flebobag ringer-lactate, sennoside a+b, urea, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left lobe of liver and porta hepatis lymphadenopathy. The BCLC stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 18 Apr 2013 (Day 1), treatment with study drug was initiated.

On 24 Apr 2013 (Day 7), the subject was hospitalized for abdominal pain (Grade 3) and the study drug was interrupted due to this event. Laboratory tests showed amylase 149 U/L (NR: 40 – 125), AST 64 U/L (NR: 7 – 38), BUN 9.282 mmol/L (NR: 2.856 – 7.497), and creatinine 119.34 umol/L (NR: 53.04 – 79.56). Abdominal CT scan ruled out acute pancreatitis. On 27 Apr 2013 (Day 10), the subject experienced pyrexia (Grade 1) and diarrhea (Grade 1) with soft or watery stools 4 times. Treatment included carbohydrates w/potassium chloride/sodium, paracetamol, cefametazole, ringer-lactate, and lactobacillus casei. On 04 May 2013 (Day 17), the subject recovered from diarrhea. On 08 May 2013 (Day 21), the subject recovered from abdominal pain and the study drug was resumed at reduced dose of 400 mg/day due to abdominal pain on the following day (Day 22). On 16 May 2013 (Day 29), the subject recovered from fever. The Investigator considered abdominal pain serious and probably related to study drug; diarrhea and fever nonserious and possibly related to study drug.

On 19 May 2013 (Day 32), the subject experienced abdominal pain (Grade 1) and treatment was not provided. On 28 May 2013 (Day 41), the subject was withdrawn due to abdominal pain. The subject received the last dose of study drug on 27 May 2013 (Day 40). The subject did not recover from this event. The Investigator considered abdominal pain nonserious and not related to study drug but related to clinical disease progression.

On 11 Jun 2013 (Day 55), the tumor response assessment showed disease progression.

On 03 Nov 2013 (Day 200, 160 days after the last dose), the subject died due to disease progression.

Subject Number	12081009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01461-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Erythema multiforme
AE(s) Leading to Discontinuation	Erythema multiforme

An 81-year-old Japanese male was diagnosed with hepatocellular carcinoma in Feb 2010. Significant medical history included chronic gastritis, chronic hepatitis C, constipation, hypertension, hyperuricemia, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included alginic acid, allopurinol, bepotastine, betamethasone, bifidobacterium, carvedilol, clobetasol, clostridium butyricum, dexchlorpheniramine, dimeticone, esomeprazole, falkamin, gentamicin, heparinoid, lactomin, lactulose, lansoprazole, lidocaine, metoclopramide, paracetamol, prednisolone, pronase, rabeprazole, ringer-lactatis, sennoside a+b, sodium bicarbonate, sucralfate, urea, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 22 Nov 2013 (Day 1), treatment with study drug was initiated.

On 29 Nov 2013 (Day 8), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2) and on 12 Dec 2013 (Day 21), the event worsened to Grade 3. The subject was treated with urea, clobetasol, and prednisolone. On the same day (Day 21), the study drug dose was reduced to 400 mg/day due to palmar-plantar erythrodysesthesia syndrome. The subject did not recover from this event. The Investigator considered the palmar-plantar erythrodysesthesia syndrome nonserious and probably related to the study drug.

On 27 Feb 2014 (Day 98), the subject was hospitalized for erythema multiforme (Grade 3). The subject was treated with dexchlorpheniramine and prednisolone. On the same day (Day 98), the subject was withdrawn from the study due to this event. The subject received the last dose of the study drug on 26 Feb 2014 (Day 97). On 05 Mar 2014 (Day 104), the subject recovered from this event. The Investigator considered erythema multiforme serious and probably related to the study drug.

Subject Number	12081010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01474-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Pneumonia

A 70-year-old Asian male was diagnosed with hepatocellular carcinoma on 07 Oct 2013. Significant medical history included chronic hepatitis C, hypertension, insomnia, and irritable bowel syndrome. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, betamethasone, bromfenac, brotizolam, carbohydrates w/potassium chloride/sodium, cefmenoxime, clostridium butyricum, diclofenac, diflucortolone, dimeticone, escherichia coli (killed escherichia coli suspension), etizolam, fluorometholone, keishikashakuyakudaioto, levofloxacin, lidocaine, loxoprofen, moviprep, naloxone, neriproct, nutrients (ensure liquid), paracetamol, pethidine, petrolatum, pronase, rabeprazole, ringer-lactate, sennoside a+b, sodium bicarbonate, telmisartan, tetracaine, trimebutine, tropicamide, ultracet, unacid, urea, ursodeoxycholic acid, zolpidem, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 28 Nov 2013 (Day 1), treatment with study drug was initiated.

On 30 Mar 2014 (Day 123), the subject experienced pneumonia (Grade 2). On 02 Apr 2014 (Day 126), the subject was hospitalized for pneumonia with symptoms of decreased appetite, weakness in legs, and body temperature of 39.7 °C. The study drug was interrupted due to this event. On 03 Apr 2014 (Day 127), the severity of pneumonia increased to Grade 3. Chest x-ray showed an infiltrative shadow in the right lower lung field and sputum examination was positive for bacteria. Treatment included paracetamol, ringer-lactate, carbohydrates w/potassium chloride/sodium, loxoprofen, and unacid. On 08 Apr 2014 (Day 132), the severity of pneumonia improved to Grade 2. On 09 Apr 2014 (Day 133), the study drug was resumed at same dose. On 14 Apr 2014 (Day 138), the subject recovered from pneumonia. The Investigator considered pneumonia serious and not related to the study drug.

On 12 May 2014 (Day 166), the subject experienced abnormal hepatic function (Grade 2). Laboratory tests showed ALT 70 U/L (NR: 10 – 40), AST 139 U/L (NR: 10 – 43), ALP 115 U/L (NR: 43 – 115), and bilirubin 10.3 umol/L (NR: 1.7 – 18.8). On 27 May 2014 (Day 181), the study drug was interrupted due to abnormal hepatic function. Treatment was not provided. On 12 Jun 2014 (Day 197), the study drug was resumed at reduced dose of 400 mg/day due to abnormal hepatic function. On 09 Jul 2014 (Day 224), the study drug was interrupted again due to abnormal hepatic function. On 16 Jul 2014 (Day 231), the study drug was resumed with reduced frequency of 400 mg every other day due to abnormal hepatic function. The subject did not recover from this event. The Investigator considered abnormal hepatic function nonserious and probably related to the study drug.

On 15 Oct 2014 (Day 322), the severity of abnormal hepatic function worsened to Grade 3 and the study drug was interrupted due to this event. Laboratory reports showed ALT 86 U/L (NR: 4 – 43), AST 198 U/L (NR: 7 – 38). On 22 Oct 2014 (Day 329), the severity of abnormal hepatic function improved to Grade 2 with ALT 79 U/L (NR: 4 – 43) and AST 181 U/L (NR: 7 – 38). On 23 Oct 2014 (Day 330), the tumor response assessment showed disease progression. On 29 Oct 2014 (Day 336), the subject was withdrawn from study due to disease progression and the subject received the last dose of study drug on 14 Oct 2014 (Day 321). The subject did not recover from abnormal hepatic function. The Investigator considered abnormal hepatic function nonserious and probably related to the study drug.

On 23 Nov 2014 (Day 361, 40 days after the last dose), the subject died due to disease progression.

Subject Number	12111002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01386-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Tumour haemorrhage

A 51-year-old Japanese male was diagnosed with hepatocellular carcinoma on 20 Feb 2013. Significant medical history included anemia, chronic hepatitis C, hypertension, and insomnia. Previous anticancer therapies included hepatectomy and radiofrequency ablation. Prior and concomitant medications included butenafine, carbohydrates w/potassium chloride/sodium, cefotaxime, clobetasol, dimeticone, heparinoid, hyoscine, lidocaine, lorazepam, loxoprofen, magnesium oxide, neurobion, omeprazole, oxycodone, paracetamol, prochlorperazine, pronase, rebamipide, ringer-lactatis, sodium bicarbonate, sodium picosulfate, trazodone, triamcinolone, ursodeoxycholic acid, valsartan, veen 3g, veen d, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver and mass at omentum. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 15 Aug 2013 (Day 1), treatment with study drug was initiated.

On 25 Aug 2013 (Day 11), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2). On 30 Aug 2013 (Day 16), the severity of palmar-plantar erythrodysesthesia syndrome worsened to Grade 3 and the study drug was interrupted. Treatment included clobetasol. On 13 Sep 2013 (Day 30), the severity of this event improved to Grade 1 and on following day (Day 31), the study drug was resumed at reduced dose of 400 mg/day due to palmar-plantar erythrodysesthesia syndrome. On 27 Sep 2013 (Day 44), the severity of palmar-plantar erythrodysesthesia syndrome worsened to Grade 2. On 18 Oct 2013 (Day 65), the subject recovered from this event. The Investigator considered this event nonserious and probably related to study drug.

On 08 Oct 2013 (Day 55), the tumor response assessment showed disease progression.

On 08 Oct 2013 (Day 55), the subject experienced malignant ascites (Grade 2). Laboratory reports showed ALT 39 U/L (NR: 10 – 40), AST 53 U/L (NR: 10 – 43), ALP 141 U/L (NR: 43 – 115), albumin 40 g/L (NR: 35 – 55), and total bilirubin 9.9 umol/L (NR: 1.7 – 18.8). Treatment was not provided and the study drug dose did not change. On 22 Nov 2013 (Day 100), the subject recovered from malignant ascites. The Investigator considered malignant ascites nonserious, and possibly related to study drug and also related to disease progression.

On 17 Oct 2013 (Day 64), the subject experienced cancer pain (Grade 3). On 18 Oct 2013 (Day 65), the subject was hospitalized with abdominal pain and was diagnosed with intra-abdominal tumor hemorrhage (Grade 2). The study drug was interrupted due to tumor hemorrhage. Laboratory reports showed Hgb 88 g/L (NR: 138 – 166). The subject underwent abdominal paracentesis which showed bloody fluid. Treatment included cefotaxime, oxycodone,

neurobion, intravenous supplementation with ringer's lactatis, veen 3g, veen d, and carbohydrates w/potassium chloride/sodium. On 18 Oct 2013 (Day 65), the subject was withdrawn from study due to disease progression and the subject received the last dose of study drug on 17 Oct 2013 (Day 64). On 21 Oct 2013 (Day 68), repeat laboratory test showed Hgb 80 g/L (NR: 138 – 166). On 22 Oct 2013 (Day 69), the severity of tumor hemorrhage worsened to Grade 3 and the subject was transfused with packed RBCs. On 23 Oct 2013 (Day 70), the blood culture was negative for bacteria. On 31 Oct 2013 (Day 78), the subject recovered from tumor hemorrhage and severity of cancer pain improved to Grade 2. The subject did not recover from cancer pain. The Investigator considered tumor hemorrhage serious and possibly related to study drug and also related to disease progression; cancer pain nonserious and not related to study drug but related to disease progression.

On 14 May 2014 (Day 273, 209 days after the last dose), the subject died due to disease progression.

Subject Number	12131003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002576
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Lower gastrointestinal haemorrhage

A 61-year-old Japanese male was diagnosed with hepatocellular carcinoma on 05 Jul 2012. Significant medical history included colon diverticulitis, diabetes mellitus, non-alcoholic fatty liver, gallbladder polyp, hyperlipidemia, hypertension, lower gastrointestinal hemorrhage, seasonal allergy (pollenosis), and nephrolithiasis (right renal calculus). Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, bio-three, clobetasol, colyte, dequalinium, dimeticone, influenza vaccine, irbesartan, iron (ferrous fumarate), ketoprofen, levocetirizine, lidocaine, magnesium oxide, olopatadine, pa, povidone-iodine, pronase, sennoside a+b, simvastatin, sodium bicarbonate, sodium picosulfate, stick zenol, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed masses at right upper and left lower lobes of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 23 Aug 2013 (Day 1), treatment with study drug was initiated.

On 12 Dec 2014 (Day 477), the subject experienced lower gastrointestinal hemorrhage (Grade 1) with symptoms of red-colored watery stools and small amount of melena. Laboratory tests showed Hgb 136 g/L (NR: 125 – 170). On 16 Dec 2014 (Day 481), the subject was hospitalized for lower gastrointestinal hemorrhage (Grade 3), and a large bowel endoscopy confirmed the diagnosis. Repeat laboratory tests showed Hgb 80 g/L (NR: 135 – 168). On 17 Dec 2014 (Day 482), the study drug was interrupted due to this event. On the same day (Day 482), repeat laboratory test showed Hgb 66 g/L (NR: 135 – 168), and the subject was transfused with packed RBC and was also treated with iron (ferrous fumarate). On 18 Dec 2014 (Day 483), repeat laboratory test showed Hgb 82 g/L (NR: 135 – 168). On 19 Dec 2014 (Day 484), the event improved to Grade 1 and later that day (Day 484), the subject was discharged from the hospital and the study drug was resumed at reduced dose of 400 mg/day due to lower gastrointestinal hemorrhage. On 05 Mar 2015 (Day 560), the subject recovered from the event with Hgb 146 g/L (NR: 125 –170). The Investigator considered lower gastrointestinal hemorrhage serious and possibly related to study drug.

The subject remained in the study at the time of data cut-off.

Subject Number	12141004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01380-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Device related infection
AE(s) Leading to Discontinuation	Device related infection

A 76-year-old Japanese male was diagnosed with hepatocellular carcinoma on 09 Feb 2012. Significant medical history included alcohol cirrhosis, colon cancer, diabetes mellitus, esophageal varices, gastroduodenal ulcer, hyperlipidemia, hyperuricemia, knee osteoarthritis, lower limb cellulitis, psoriasis vulgaris, seborrheic dermatitis, and stasis dermatitis. Previous anticancer therapies included radiofrequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included allopurinol, amino acids w/electrolytes/glucose/thiamine hydrochloride, betamethasone, carbohydrates w/potassium chloride/sodium, cefazolin, celecoxib, clindamycin, clobetasol, doripenem, ephedrine, epinephrine, eufusol, ezetimibe, famotidine, fenofibrate, fentanyl, flurbiprofen, gentamicin, glycerol, human insulin, lidocaine, magnesium oxide, menatetrenone, naloxone, neomycin, neurobion, phenylephrine, potacol r, primaxin, propofol, rebamipide, remifentanil, rocuronium, ropivacaine, sennoside a+b, solita-t1, sugammadex, sulperazon, teicoplanin, urea, ursodeoxycholic acid, voglibose, and white soft paraffin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at caudate and left lobes of the liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 27 Sep 2013 (Day 1), treatment with study drug was initiated.

On 04 Oct 2013 (Day 8), the subject experienced hepatic dysfunction (Grade 2) with total bilirubin 46.17 umol/L (NR: 3.42 – 17.1) and ammonia 124 umol/L (NR: 8 – 35). On the same day (Day 8), the study drug was interrupted due to hepatic dysfunction. The Investigator considered hepatic dysfunction nonserious and possibly related to study drug.

On 07 Oct 2013 (Day 11), the subject was hospitalized for device related infection (right artificial knee joint infection; Grade 3). The subject also experienced worsening of hepatic dysfunction (Grade 3) with total bilirubin 64.98 umol/L (NR: 3.42 – 17.1). On 09 Oct 2013 (Day 13), the subject underwent wound debridement of the right knee. The subject was treated with sulperazon, ephedrine, famotidine, flurbiprofen, teicoplanin, cefazolin, celecoxib, clindamycin, and doripenem. On 11 Oct 2013 (Day 15), laboratory tests showed albumin 20 g/L (NR: 35 – 55), platelets 53 x10^9/L (NR: 167 – 362), lipase 116 U/L (NR: 13 – 60), and total bilirubin 33 umol/L (NR: 1.7 – 18.8). On 15 Oct 2013 (Day 19), the subject recovered from hepatic dysfunction with total bilirubin 27.36 umol/L (NR: 3.42 – 17.1). On 31 Oct 2013 (Day 35), the subject was withdrawn from the study due to device related infection. The subject received the last dose of the study drug on 04 Oct 2013 (Day 8). On 28 Jan 2014 (Day 124), severity of device related infection improved to Grade 2. The subject was recovering from device related infection. The Investigator considered device related

infection serious and possibly related to the study drug; hepatic dysfunction nonserious and possibly related to study drug.

On 04 Feb 2014 (Day 131), the tumor response assessment showed disease progression.

On 04 Aug 2014 (Day 312, 304 days after the last dose), the subject died of unknown cause.

Subject Number	12141021
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000779
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Jaundice cholestatic, Cholangitis, Liver abscess

A 74-year-old Japanese male was diagnosed with hepatocellular carcinoma in 2008. Significant medical history included anemia, diabetes mellitus, erosive duodenitis, cholelithiasis, gastritis, hepatitis B, insomnia, and hepatic cirrhosis. Previous anticancer therapies included regional chemotherapy, hyperthermia therapy, percutaneous ethanol injection therapy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included aczym, cefcapene, ceftriaxone, cimetidine, dexamethasone, diclofenac, difluprednate, doripenem, esomeprazole, eufusol, famotidine, flurbiprofen, gabexate, garenoxacin, glucagon, haloperidol, human albumin, hyoscine, juzentaihoto, loxoprofen, metamizole, metformin, metoclopramide, midazolam, mosapride, neurobion, osmosal, paracetamol, pronase, propofol, rebamipide, sitafloxacin, solita-t1, urea, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe and mass at right upper lobe of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 12 Sep 2014 (Day 1), treatment with study drug was initiated.

On 07 Oct 2014 (Day 26), the subject was hospitalized for cholestatic jaundice (Grade 3) and the study drug was interrupted due to cholestatic jaundice. Laboratory tests showed ALT 238 U/L (NR: 10 – 40), AST 242 U/L (NR: 10 – 43), ALP 568 U/L (NR: 43 – 115), total bilirubin 136.3 umol/L (NR: 0 – 18.8), and GGT 613 U/L (NR: 10 – 49). Abdominal endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP) showed obstructive jaundice due to tumorous lesion obstructing the bile duct. The subject underwent insertion of endoscopic nasobiliary drainage tube. On 10 Oct 2014 (Day 29), the subject underwent removal of endoscopic nasobiliary drainage tube, plastic stent placement in the obstruction area, and had endoscopic ultrasound with fine needle aspiration of the pancreatic head. On 12 Oct 2014 (Day 31), the subject was discharged from the hospital. On 22 Oct 2014 (Day 41), laboratory results showed ALT 19 U/L, AST 25 U/L, ALP 160 U/L, GGT 96 U/L, and total bilirubin 15.9 umol/L. On the same day (Day 41), the subject was recovered from cholestatic jaundice and study drug was resumed at the same dose. The Investigator considered cholestatic jaundice serious and not related to the study drug.

On 13 Nov 2014 (Day 63), the subject experienced cholangitis (Grade 3) and on 14 Nov 2014 (Day 64), the subject experienced abdominal pain (Grade 2). The subject was treated with eufusol, loxoprofen, cefcapene, aczym, and esomeprazole. On 22 Nov 2014 (Day 72), the subject was hospitalized for ongoing cholangitis and liver abscess (Grade 3) and the study drug was interrupted due to these events. The subject underwent ERCP to remove the stent and endoscopic nasobiliary drainage tube was placed. On 25 Nov 2014 (Day 75), blood culture result was positive with gram-negative bacillus. Treatment included ceftriaxone,

metoclopramide, flurbiprofen, diclofenac, doripenem, paracetamol, garenoxacin, sitafloxacin, and metamizole. On 04 Dec 2014 (Day 84), the subject underwent repeat ERCP and endoscopic nasobiliary drainage tube was removed and replaced by bile duct metallic stent. On 17 Dec 2014 (Day 97), the study drug was resumed at same dose. On 25 Dec 2014 (Day 105), laboratory tests showed WBC 10.3 x10^9/L (NR: 3.9 – 9.3) and CRP 148.76 mg/L (NR: 0 – 3). On 26 Dec 2014 (Day 106), the CT of abdomen showed aggravation of the liver abscess. The subject underwent ERCP and endoscopic nasobiliary drainage tube was placed. On 24 Jan 2015 (Day 135), the subject recovered from cholangitis and did not recover from liver abscess and abdominal pain. The Investigator considered cholangitis and liver abscess serious and not related to the study drug; abdominal pain nonserious and possibly related to the study drug.

On 26 Dec 2014 (Day 106), tumor response assessment showed disease progression and received the last dose of the study drug on 25 Dec 2014 (Day 105). On 13 Jan 2015 (Day 124), the subject was withdrawn from study due to disease progression.

On 07 Jul 2015 (Day 299, 194 days after the last dose), the subject died due to disease progression.

Subject Number	12141025
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006840
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy
AE(s) Leading to Discontinuation	Fatigue

A 68-year-old Japanese male was diagnosed with hepatocellular carcinoma on 01 Oct 2014. Significant medical history included large intestine polyp, cancer pain, cholelithiasis, chronic gastritis, constipation, contrast media allergy (iodine), esophageal varices, hemorrhoids, hepatitis C, gastric polyps, hepatic cirrhosis, insomnia, and splenomegaly. Previous anticancer therapy included radiotherapy to the thoracic vertebra Th12. Prior and concomitant medications included amino acids w/vitamins, betamethasone, brotizolam, cefpodoxime, celecoxib, denosumab, diazepam, difluprednate, docusate, falkamin, furosemide, glucose, levocetirizine, lidocaine, loxoprofen, lubiprostone, magnesium oxide, oxycodone, pronase, rabeprazole, rebamipide, sennoside a+b, spironolactone, super cal, terufis, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed masses at right lower and middle lobes of lung and MRI showed masses at thoracic vertebrae, right 9th and 12th ribs; para-aortic lymphadenopathy; and lesions at right and left liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 09 Dec 2014 (Day 26), the subject experienced decreased platelet count (Grade 3) with platelet count 53 x10^9/L (NR: 125 – 375) and the study drug dose was reduced to 400 mg/day due to the event. On 16 Dec 2014 (Day 33), severity of decreased platelet count improved to Grade 2. On 24 Dec 2014 (Day 41), the subject recovered from decreased platelet count with platelet count 84 x10^9/L. The Investigator considered decreased platelet count nonserious and probably related to the study drug.

On 17 Feb 2015 (Day 96), the subject experienced fatigue (Grade 2). On 14 Apr 2015 (Day 152), the subject experienced abnormal hepatic function (Grade 2) and fatigue worsened to Grade 3. On the same day (Day 152), the subject was withdrawn from the study due to clinical disease progression and received the last dose of the study drug on 13 Apr 2015 (Day 151). Laboratory tests showed AST 276 U/L (NR: 7 – 40), ALT 46 U/L (NR: 0 – 35), total bilirubin 25.65 umol/L (NR: 3.42 – 17.1), and ALP 417 U/L (NR: 85 – 300). The subject was treated with betamethasone. The subject did not recover from abnormal hepatic function and fatigue. The Investigator considered abnormal hepatic function and fatigue nonserious and not related to the study drug but related to disease progression.

On 27 Apr 2015 (Day 165), tumor response assessment showed disease progression.

On 12 May 2015 (Day 180), the subject experienced hepatic encephalopathy (Grade 3). Laboratory tests showed AST 159 U/L, ALP 543 U/L, albumin 29 g/L (NR: 36 – 55), and

ammonia 128 umol/L (NR: 8 – 35). On 13 May 2015 (Day 181), the subject was hospitalized for this event and was treated with glucose, terufis, and amino acids w/vitamins. On 02 Jun 2015 (Day 201), repeat laboratory tests showed albumin 27 g/L, AST 150 U/L, ALT 56 U/L, ALP 486 U/L, and ammonia 131 umol/L. On 03 Jun 2015 (Day 202), hepatic encephalopathy improved to Grade 2. The subject was recovering from the event. The Investigator considered hepatic encephalopathy serious and not related to the study drug but related to disease progression.

On 18 Jun 2015 (Day 217, 66 days after the last dose), the subject died due to disease progression.

Subject Number	12151007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000624
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Lower gastrointestinal haemorrhage (2x), Ascites, Oesophageal varices haemorrhage
AE(s) Leading to Discontinuation	Oesophageal varices haemorrhage

A 71-year-old Japanese male was diagnosed with hepatocellular carcinoma on 20 Apr 2012. Significant medical history included benign prostatic hyperplasia, cancer pain, chronic hepatitis C, constipation, dry eye, esophageal varices, gastroesophageal reflux disease, hepatic cirrhosis, intervertebral disc protrusion, and neuralgia. Previous anticancer therapies included high frequency ablation, transcatheter arterial chemoembolization, and radiotherapy to sacral lesion. Prior and concomitant medication included, aminoleban, amitriptyline, azosemide, betamethasone, carbohydrates w/potassium chloride/sodium, celecoxib, cinal, dexamethasone, diclofenac, dimeticone, diphenhydramine, duloxetine, epinastine, falkamin, faropenem, furosemide, heparinoid, human albumin, hyaluronic acid, hydrocortisone, indometacin, lactomin, lansoprazole, levofloxacin, lidocaine, liver hydrolysate, loperamide, luliconazole, metoclopramide, midazolam, naproxen, neurobion, omeprazole, oxycodone, pentazocine, posterisan f, pregabalin, prochlorperazine, pronase, rabeprazole, rebamipide, retinol, sennoside a+b, shakuyakukanzoto, spironolactone, tamsulosin, tolterodine, tolvaptan, ultracet, urea, ursodeoxycholic acid, veen d, and white soft paraffin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes and sacral mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 18 Sep 2014 (Day 63), the subject experienced lower gastrointestinal hemorrhage (Grade 2). On 26 Sep 2014 (Day 71), the subject experienced anemia (Grade 2) with Hgb 91 g/L (NR: 130 – 175). On 30 Sep 2014 (Day 75), the study drug was interrupted due to lower gastrointestinal hemorrhage. On 01 Oct 2014 (Day 76), the study drug remained interrupted due to anemia. On 03 Oct 2014 (Day 78), the subject was hospitalized for worsening of lower gastrointestinal hemorrhage (Grade 3). On 06 Oct 2014 (Day 81), colonoscopy showed colitis of sigmoid colon with slightly edematous mucosa accompanied with significant redness which was considered to be a bleeding spot. The subject was treated with posterisan f and human albumin. On 10 Oct 2014 (Day 85), the severity of lower gastrointestinal hemorrhage improved to Grade 1. On 21 Oct 2014 (Day 96), the subject recovered from lower gastrointestinal hemorrhage and was discharged from the hospital. The subject did not recover from anemia. The Investigator considered lower gastrointestinal hemorrhage serious and not related to study drug; and anemia nonserious and not related to the study drug.

On 29 Oct 2014 (Day 104), the subject experienced ascites (Grade 2) confirmed via abdominal ultrasound and the study drug remained interrupted due to this event. On 31 Oct 2014

(Day 106), the subject was re-hospitalized for lower gastrointestinal hemorrhage (Grade 3). Laboratory tests showed RBC 2.67 x10^12/L (NR: 4.2 – 5.7) and Hgb 79 g/L. The subject underwent abdominal cavity drainage and was transfused with packed red blood cell. On 01 Nov 2014 (Day 107), the lower gastrointestinal hemorrhage improved to Grade 2 and the subject was discharged from the hospital. The subject was recovering from lower gastrointestinal hemorrhage and did not recover from ascites. The Investigator considered lower gastrointestinal hemorrhage serious and not related to study drug; ascites nonserious and not related to study drug.

On 14 Nov 2014 (Day 120), repeat abdominal ultrasound showed large amount of ascites. On 18 Nov 2014 (Day 124), the subject was re-hospitalized for worsening of ascites (Grade 3). The subject was treated with posterisan f, human albumin, furosemide, azosemide, and tolvaptan. On 25 Nov 2014 (Day 131), the subject recovered from ascites confirmed by the abdominal ultrasound. On 27 Nov 2014 (Day 133), the study drug was resumed at a reduced dose of 400 mg/day due to lower gastrointestinal hemorrhage. The subject was discharged from the hospital on 27 Nov 2014 (Day 133). However, later that day (Day 133), the subject had hematemesis. An endoscopy was performed and stimulation of camera insertion triggered a large volume of hematemesis. The subject was re-hospitalized for esophageal varices hemorrhage (Grade 3). Treatment included venous ligation, packed red blood cells transfusion, omeprazole, neurobion, midazolam, and veen d. On 28 Nov 2014 (Day 134), the subject was withdrawn from the study due to esophageal varices hemorrhage. The subject received the last dose of study drug on 27 Nov 2014 (Day 133). On 02 Dec 2014 (Day 138), subject's esophageal varices hemorrhage improved to Grade 2. On 05 Dec 2014 (Day 141), laboratory tests showed RBC 2.83 x10^12/L (NR: 4 – 5.6) and Hgb 82 g/L (NR: 125 – 170). On the same day (Day 141), tumor response assessment showed disease progression. On 10 Dec 2014 (Day 146), the subject recovered from esophageal varices hemorrhage. The Investigator considered ascites and esophageal varices hemorrhage serious and not related to study drug but related to disease progression.

On 06 Jul 2015 (Day 354, 221 days after the last dose), the subject died due to disease progression.

Subject Number	12151008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01572-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Ascites

An 82-year-old Japanese male was diagnosed with hepatocellular carcinoma on 08 Feb 2010. Significant medical history included arteriosclerosis, chronic gastritis, esophageal varices, gastric varices, hepatitis C, hypertension, insomnia, and hepatic cirrhosis. Previous anticancer therapies included hepatectomy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included bifidobacterium, canrenoic acid, carbohydrates w/potassium chloride/sodium, ceftriaxone, difluprednate, dimeticone, esomeprazole, falkamin, furosemide, gluaceto, human albumin, lidocaine, loperamide, magnesium oxide, midazolam, neurobion, nifedipine, pronase, retinol, rilmazafone, spironolactone, tolvaptan, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and mass at right kidney. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 29 Jul 2014 (Day 1), treatment with study drug was initiated.

On 07 Aug 2014 (Day 10), the subject experienced diarrhea (Grade 2) and bacterial peritonitis (Grade 3). The subject was treated with loperamide, bifidobacterium, and ceftriaxone. On 11 Aug 2014 (Day 14), laboratory tests showed albumin 35 g/L (NR: 35 – 55), total protein 86 g/L (NR: 60 – 80), and CRP 20.1 mg/L (NR: 0 – 5). On 19 Aug 2014 (Day 22), the study drug was interrupted due to diarrhea. On 25 Aug 2014 (Day 28), the subject was diagnosed with abnormal hepatic function (Grade 2). On the same day (Day 28), the subject recovered from diarrhea. The study drug remained interrupted due to abnormal hepatic function. Laboratory tests showed albumin 33 g/L, total bilirubin 23.8 umol/L (NR: 1.7 – 18.8), ALP 155 U/L (NR: 43 – 115), ALT 28 U/L (NR: 10 – 40), AST 102 U/L (NR: 10 – 43), total protein 82 g/L, and GGT 56 U/L (NR: 10 – 49). The subject did not recover from abnormal hepatic function and bacterial peritonitis. The Investigator considered diarrhea and abnormal hepatic function nonserious and possibly related to the study drug; bacterial peritonitis nonserious and not related to the study drug.

On 29 Aug 2014 (Day 32), the subject experienced ascites (unspecified; Grade 1) and on 31 Aug 2014 (Day 34), the subject experienced constipation (Grade 2). On 05 Sep 2014 (Day 39), the subject was hospitalized for worsening of ascites (Grade 3). Endoscopy showed esophageal varices (Grade 2). On 09 Sep 2014 (Day 43), laboratory tests showed albumin 33 g/L, ALP 131 U/L, ALT 54 U/L, AST 208 U/L, and total bilirubin 28.9 umol/L. The subject underwent abdominal paracentesis and was treated with human albumin, canrenoic acid, falkamin, furosemide, magnesium oxide, spironolactone, and tolvaptan. The study drug remained interrupted due to diarrhea and abnormal hepatic function; and was not resumed. On 10 Sep 2014 (Day 44), severity of ascites improved to Grade 2. On 16 Sep 2014 (Day 50), tumor response assessment showed disease progression. On the same day (Day 50), the subject was

withdrawn from the study due to disease progression. The subject received the last dose of the study drug on 19 Aug 2014 (Day 22). The subject did not recover from ascites, constipation, and esophageal varices. The Investigator considered ascites serious and not related to the study drug but related to disease progression; constipation and esophageal varices nonserious and not related to the study drug.

On 28 Oct 2014 (Day 92, 70 days after the last dose), the subject died due to disease progression.

Subject Number	12191010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01526-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Drug eruption
AE(s) Leading to Discontinuation	Dermatitis

A 41-year-old Japanese female was diagnosed with hepatocellular carcinoma on 05 Nov 2013. Significant medical history included anemia, atopic dermatitis, hypercarotinemia, chronic gastritis, chronic hepatitis B, cholelithiasis, hemorrhoids, hypotension, hepatic cirrhosis, ovarian cyst, and post procedural pneumonia. Previous anticancer therapies included transcatheter arterial chemoembolization, regional chemotherapy (hepatic intra-arterial chemotherapy), high frequency ablation, and radiotherapy to right liver lobe mass. Prior and concomitant medications included asphagen, bepotastine, diflucortolone, difluprednate, dimeticone, entecavir, falkamin, heparin, heparinoid, hydrocortisone, iron, lidocaine, prednisolone, pronase, rabeprazole, sekicode, sodium bicarbonate, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, left lingular lung mass, and bilateral lung masses. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 14 Jun 2014 (Day 12), the subject was hospitalized for drug eruption (generalized papuloerythematous drug eruption; Grade 3) with symptoms of severe itching throughout the subject's body including lips and buccal mucosa. The subject was treated with asphagen, bepotastine, diflucortolone, and prednisolone. On 16 Jun 2014 (Day 14), the study drug was interrupted due to drug eruption. On 19 Jun 2014 (Day 17), the drug eruption improved to Grade 1. On 20 Jun 2014 (Day 18), the subject was discharged from the hospital. On 04 Jul 2014 (Day 32), the subject recovered from drug eruption. On 11 Jul 2014 (Day 39), the study drug was resumed at the same dose. The Investigator considered drug eruption serious and possibly related to the study drug.

On 12 Jul 2014 (Day 40), the subject experienced dermatitis (study drug induced dermatitis; Grade 1). The subject was treated with bepotastine and the subject was withdrawn from the study due to dermatitis on the same day (Day 40). The subject received the last dose of study drug on the same day (Day 40). On 05 Aug 2014 (Day 64), the subject recovered from dermatitis. The Investigator considered dermatitis nonserious and probably related to the study drug.

On 22 Aug 2016 (Day 812, 772 days after the last dose), the subject died due to disease progression.

Subject Number	12211001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01318-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Psoriasis, Palmar-plantar erythrodysaesthesia syndrome

A 78-year-old Japanese male was diagnosed with hepatocellular carcinoma on 09 Jun 2010. Significant medical history included aortic aneurysm, chronic hepatitis C, constipation, drug abuse (methamphetamine), dyslipidemia, food allergy (mackerel), gastritis, gastric ulcer, hepatic cirrhosis, hypertension, insomnia, pancreatic cyst, psoriasis, and type 2 diabetes mellitus. Previous anticancer therapies included radiofrequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included albumin tannate, betamethasone, bifidobacterium, calcipotriol, clostridium butyricum, dimeticone, hyoscine, lansoprazole, lidocaine, loperamide, miglitol, paracetamol, pirenoxine, pronase, sulfadiazine, telmisartan, terbinafine, urea, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at caudate and left lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 04 Jul 2013 (Day 1), treatment with study drug was initiated.

On 10 Jul 2013 (Day 7), the subject was hospitalized for exacerbation of psoriasis (Grade 2). On 12 Jul 2013 (Day 9), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 1). The subject was treated with betamethasone, calcipotriol, paracetamol, and urea. On 24 Jul 2013 (Day 21), psoriasis improved to Grade 1. The subject was discharged from the hospital. On 31 Oct 2013 (Day 120), the subject recovered from palmar-plantar erythrodysesthesia syndrome and exacerbation of psoriasis. The Investigator considered exacerbation of psoriasis and palmar-plantar erythrodysesthesia syndrome serious and probably related to the study drug.

On 17 Oct 2013 (Day 106), tumor response assessment showed disease progression. On 24 Oct 2013 (Day 113), the subject was withdrawn from the study due to disease progression, and the last dose of the study drug was received on 23 Oct 2013 (Day 112).

On 08 Jan 2014 (Day 189, 77 days after the last dose), the subject died due to disease progression.

Subject Number	12211002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01329-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Fatigue, Platelet count decreased
AE(s) Leading to Discontinuation	Fatigue, Platelet count decreased

A 78-year-old Japanese female was diagnosed with hepatocellular carcinoma on 07 Mar 2000. Significant medical history included aortic aneurysm, chronic gastritis, chronic hepatitis C, constipation, hepatic cirrhosis, hypertension, hypothyroidism, lumbar disc herniation, osteoporosis, gastroesophageal reflux disease, trigeminal neuralgia, and varicose veins of lower extremities. Previous anticancer therapies included high frequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/electrolytes/glucose/thiamine (bfluid), betamethasone, bisacodyl, diclofenac, dimeticone, eldecalcitol, furosemide, glycerol, guaiazulene, hyoscine, levofloxacin, levothyroxine, lidocaine, magnesium oxide, metoclopramide, olmesartan, paracetamol, pregabalin, pronase, ringer-lactatis, sennoside a+b, shakuyakukanzoto, sodium picosulfate, spironolactone, urea, ursodeoxycholic acid, and veen d. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes and right portal vein. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 22 Jul 2013 (Day 4), the subject experienced fatigue (Grade 2) and pyrexia (Grade 1). On 25 Jul 2013 (Day 7), the subject experienced lower gastrointestinal hemorrhage (Grade 3) with Hgb 114 g/L (NR: 113 – 152). On 29 Jul 2013 (Day 11), the subject was hospitalized for fatigue (Grade 3) and the study drug dose was reduced to 400 mg/day due to fatigue. On 31 Jul 2013 (Day 13), the subject also experienced decreased platelet count (Grade 4) with a platelet count 24 x10^9/L (NR: 130 – 369) and generalized erythema (Grade 1). See table below. The study drug was interrupted due to fatigue, decreased platelet count, and generalized erythema. The subject was treated with oxygen supplementation, ringer lactatis, veen d, amino acids w/electrolytes/glucose/thiamine (bfluid), and betamethasone. On 01 Aug 2013 (Day 14), colonoscopy showed bleeding from the capillaries of the ascending colon and was treated with argon plasma coagulation. On 02 Aug 2013 (Day 15), the subject was treated with platelet transfusion. On 03 Aug 2013 (Day 16), the subject recovered from pyrexia. On 04 Aug 2013 (Day 17), the subject experienced anemia (Grade 3) with Hgb 71 g/L. On 06 Aug 2013 (Day 19), the subject experienced delirium (Grade 2). On 07 Aug 2013 (Day 20), the subject was transfused with packed red blood cell. On 08 Aug 2013 (Day 21), the decreased platelet count improved to Grade 3 and the subject recovered from lower gastrointestinal hemorrhage. On 13 Aug 2013 (Day 26), the subject recovered from generalized erythema. On 22 Aug 2013 (Day 35), the subject recovered from fatigue and decreased platelet count with platelet count 129x10^9/L. On 22 Aug 2013 (Day 35), the subject was withdrawn from the study due to fatigue and decreased platelet count. The subject received the last dose of the study drug on 30 Jul 2013 (Day 12). On 26 Aug 2013 (Day 39), the anemia improved to Grade 2.

The subject did not recover from anemia and delirium. The Investigator considered fatigue and decreased platelet count serious and probably related to the study drug; lower gastrointestinal hemorrhage, anemia, generalized erythema, and pyrexia nonserious and probably related to the study drug; delirium nonserious and not related to the study drug.

On 06 Sep 2013 (Day 50), tumor response assessment showed disease progression.

On 05 Feb 2015 (Day 567, 555 days after the last dose), the subject died due to disease progression.

Table Platelet Count

Laboratory Test Date (Day)	**Platelet Count Central Laboratory NR: 125 – 375 x10^9/L Local Laboratory NR: 130 – 369 x10^9/L**
16 Jul 2013 (Day –3) (Screening)	123 CNR
25 Jul 2013 (Day 7)	100 LNR
31 Jul 2013 (Day 13)	24 LNR
02 Aug 2013 (Day 15)	20 LNR
07 Aug 2013 (Day 20)	22 LNR
08 Aug 2013 (Day 21)	28 LNR
12 Aug 2013 (Day 25)	87 LNR
19 Aug 2013 (Day 32)	136 CNR
22 Aug 2013 (Day 35)	129 LNR
26 Aug 2013 (Day 39)	189 CNR

CNR = Central Laboratory Normal Range
LNR = Local Laboratory Normal Range

Subject Number	12211004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01370-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Jaundice cholestatic

A 75-year-old Japanese male was diagnosed with hepatocellular carcinoma in Sep 2005. Significant medical history included chronic gastritis, chronic hepatitis C, gastric ulcer, and hepatic cirrhosis. Previous anticancer therapies included microwave therapy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included betamethasone, dimeticone, hyoscine, lidocaine, pronase, sennoside a+b, sodium picosulfate, tsukushi, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and lymphadenopathy at porta-hepatis. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 01 Aug 2013 (Day 1), treatment with study drug was initiated.

On 05 Aug 2013 (Day 5), the subject experienced abnormal hepatic function (Grade 3) with AST 120 U/L (NR: 10 – 35), ALT 108 U/L (NR: 5 – 40), and total bilirubin 63.27 umol/L (NR: 3.42 – 17.1). On the same day (Day 5), the study drug was interrupted due to the event. On 12 Aug 2013 (Day 12), ultrasound of abdomen showed no change in severity of bile duct stenosis from previous CT scan. On 14 Aug 2013 (Day 14), the subject recovered from the event with AST 55 U/L (NR: 10 – 43) and ALT 43 U/L. (NR: 10 – 40) The Investigator considered abnormal hepatic function nonserious and possibly related to the study drug.

On 19 Aug 2013 (Day 19), the subject was hospitalized for cholestatic jaundice (Grade 3) with total bilirubin of 104.31 umol/L. The subject also experienced bile duct stenosis (Grade 2) which was ongoing since 26 Jul 2013 (Day −6) as Grade 1. The study drug remained interrupted due to these events. On 02 Sep 2013 (Day 33), the severity of bile duct stenosis worsened to Grade 3 with total bilirubin 100.89 umol/L and magnetic resonance cholangiopancreatography showed porta-hepatis bile duct stenosis. On 20 Sep 2013 (Day 51), tumor response assessment showed disease progression and the subject was withdrawn from study due to disease progression. The subject received the last dose of the study drug on 05 Aug 2013 (Day 5). On the same day (Day 51), the subject had endoscopic retrograde cholangiopancreatography, but tube was not placed since the insertion of guided wire from left porta-hepatis bile duct stenosis into peripheral part could not be achieved. On 25 Sep 2013 (Day 56), the subject had percutaneous transhepatic cholangiography drainage and underwent insertion of bile duct stent and biliary drainage tube. The subject was also treated with betamethasone. On 02 Oct 2013 (Day 63), the subject recovered from cholestatic jaundice. On 11 Oct 2013 (Day 72), cholangiography did not show any obstruction and biliary drainage tube was removed. On 16 Oct 2013 (Day 77), the subject was discharged from the hospital. The subject did not recover from bile duct stenosis. The Investigator considered cholestatic

jaundice serious and not related to the study drug; bile duct stenosis nonserious and not related to the study drug.

On 22 Mar 2015 (Day 599, 594 days after the last dose), the subject died due to unknown cause.

Subject Number	12221001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01271-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Hepatic function abnormal, Pyrexia, Ascites

A 57-year-old Japanese female was diagnosed with hepatocellular carcinoma in Apr 2008. Significant medical history included acute hepatitis, cerebral infarction, chronic hepatitis B, chronic hepatitis C, constipation, disseminated intravascular coagulation, dyspepsia, edema due to hepatic disease, hypoalbuminemia, hypocalcemia, insomnia, hepatic cirrhosis, portal hypertensive gastropathy, and uterine leiomyoma. Previous anticancer therapies included hepatic intra-arterial chemotherapy(2x), hepatectomy, microwave ablation, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included brotizolam, clobetasol, dimeticone, falkamin, flavine adenine dinucleotide, flomoxef, furosemide, glucose, glycyrrhizic acid, hangeshashinto, human albumin, hyaluronic acid, indigo carmine, levofloxacin, lidocaine, loxoprofen, magnesium oxide, naphazoline, pronase, rabeprazole, sodium chloride, sodium phosphate, spironolactone, teprenone, urea, ursodeoxycholic acid, and white soft paraffin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 29 Mar 2013 (Day 1), treatment with study drug was initiated.

On 06 Apr 2013 (Day 9), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 3) and was treated with clobetasol and white soft paraffin (white petrolatum). On 12 Apr 2013 (Day 15), study drug dose was reduced to 400 mg/day due to the event. On 22 May 2013 (Day 55), subject recovered from this event. The Investigator considered palmar-plantar erythrodysesthesia syndrome nonserious and probably related to the study drug.

On 18 Apr 2013 (Day 21), the subject experienced diarrhea (Grade 2). On 07 May 2013 (Day 40), the subject was hospitalized for abnormal hepatic function (Grade 3). On same day (Day 40), the subject also experienced hypoalbuminemia (Grade 2). Laboratory tests showed ALP 139 U/L (NR: 30 – 115), ALT 153 U/L (NR: 10 – 33), AST 219 U/L (NR: 10 – 36), and albumin 26 g/L (NR: 35 – 55). On 08 May 2013 (Day 41), the study drug was interrupted due to diarrhea and abnormal hepatic function. The subject was treated with dibasic sodium phosphate, sodium chloride, hangeshashinto, flavine adenine dinucleotide, glucose, glycyrrhizic acid, and loxoprofen. On 09 May 2013 (Day 42) the subject experienced pyrexia (Grade 1) with temperature 38 °C and ascites (Grade 2) on 16 May 2013 (Day 49). The subject's hospitalization was prolonged due to pyrexia and ascites. The subject's CT and abdominal ultrasonography showed ascites, and the subject was treated with furosemide, flomoxef, and sodium chloride. On the same day (Day 49), tumor response assessment showed disease progression. On 21 May 2013 (Day 54), the subject was withdrawn from the study due to disease progression and received the last of study drug on 07 May 2013 (Day 40). The subject recovered from diarrhea on 26 May 2013 (Day 59) and recovered from abnormal hepatic

function, pyrexia, and ascites on 13 Jun 2013 (Day 77). The subject did not recover from hypoalbuminemia. The Investigator considered abnormal hepatic function, pyrexia and ascites serious and probably related to the study drug and related to disease progression; hypoalbuminemia nonserious and probably related to the study drug but related to disease progression; diarrhea nonserious and probably related to the study drug.

On 22 Mar 2014 (Day 359, 319 days after the last dose), the subject died due to disease progression.