On 21 Oct 2014 (Day 68), the subject experienced decreased appetite (Grade 2). On 24 Oct 2014 (Day 71), the subject experienced ascites (Grade 3). Due to persistence of decreased appetite and ascites, the subject was hospitalized. Ultrasound of abdomen showed massive ascites in the abdominal and pelvic cavity and on 26 Oct 2014 (Day 73), the study drug was reduced to 400 mg/day due to abdominal pain, decreased appetite, and ascites. The subject was treated with tramadol, paracetamol, loperamide, megestrol, ascorbic acid, potassium, nystatin, unacid, lorazepam and the subject underwent ultrasound-guided drainage. On 29 Oct 2014 (Day 76), the study drug was withdrawn due to abdominal pain and ascites. On 30 Oct 2014 (Day 77), the subject was withdrawn from the study due to clinical disease progression. The subject received the last dose of study drug on 28 Oct 2014 (Day 75). On 30 Oct 2014 (Day 77), the subject recovered from abdominal pain and did not recover from ascites and decreased appetite. The Investigator considered abdominal pain, decreased appetite, and ascites serious and not related to study drug but related to disease progression.

On 21 Nov 2014 (Day 99), the subject experienced acute respiratory failure and was treated with epinephrine and dopamine. Later that day, (Day 99, 24 days after the last dose), the subject died due to acute respiratory failure secondary to clinical disease progression. Autopsy was not performed. The Investigator considered acute respiratory failure serious and not related to study drug.

Section II Death due to Disease Progression Arm: Lenvatinib

Subject Number	24151015
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004091
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cholecystitis
Death due to PD	Unknown

A 48-year-old Chinese male was diagnosed with hepatocellular carcinoma on 12 Mar 2008. Significant medical history included cancer pain, chronic gastritis, chronic hepatitis B, hepatic cirrhosis, diabetes mellitus, and cholelithiasis. Previous anticancer therapies included radiotherapy to osseous metastasis and right adrenal metastases, hepatectomy, percutaneous ethanol injection, radio frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included adefovir, alprostadil, azintamide, codeine w/ibuprofen, fentanyl, glutathione, human albumin, human insulin, human mixtard, hyoscine, lamivudine, metoclopramide, morphine, oxycocet, pantoprazole, potassium, proliv, rabeprazole, silybum marianum, unspecified herbal and traditional medicine (chinese herb/danning), vitamin b-complex with vitamin c, and water for injection. At Screening, tumor assessments of target/non-target lesions via CT scan showed multiple masses at bilateral lungs; mass at left lobe of lung and right pulmonary door, and right ribbing; MRI showed lesions around the liver lobe, abdominal and chest wall, and right adrenal mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 19 Dec 2014 (Day 1), treatment with study drug was initiated.

On 04 Feb 2015 (Day 48), the subject experienced cholecystitis (Grade 2) confirmed by abdominal CT scan. On 13 Feb 2015 (Day 57), an abdominal ultrasound also showed cholecystitis and laboratory tests showed total bilirubin 56.8 umol/L (NR: 0 – 18.8), ALT 33 U/L (NR: 10 – 40), and AST 52 U/L (NR: 10 – 43). On the same day (Day 57), the study drug was interrupted due to this event. On 15 Feb 2015 (Day 59), the subject was hospitalized for cholecystitis and was treated fentanyl patch, alprostadil, glutathione, human insulin, metoclopramide, pantoprazole, potassium, proliv, vitamin b-complex with vitamin c, human albumin, hyoscine, morphine, silybum marianum, and unspecified herbal and traditional medicine (chinese herb/danning). On 18 Feb 2015 (Day 62) the subject recovered from cholecystitis with AST 53 U/L (NR: 15 – 40), ALT 45 U/L (NR: 9 – 50), and total bilirubin 31.2 umol/L (NR: 3.4 – 20.4), and was discharged from hospital. On 19 Feb 2015 (Day 63), the study drug was resumed at same dose. The Investigator considered cholecystitis serious and possibly related to the study drug.

On 23 Mar 2015 (Day 95), the subject was withdrawn from study due to lost to follow up and received the last dose of study drug on 13 Mar 2015 (Day 85).

On 31 Mar 2015 (Day 103, 18 days after the last dose), site found out that the subject passed away from another personnel. Details of the subject's death were unknown.

Arm: Sorafenib

Subject Number	10031006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01462-CLI-US
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Acute kidney injury
Death due to PD	Yes

A 63-year-old African American male was diagnosed with hepatocellular carcinoma on 29 Apr 2013. Significant medical history included hepatitis C, depression, and diabetes mellitus. Previous anticancer therapies included transcatheter arterial chemoembolization and radiofrequency ablation. Prior and concomitant medications included cefotaxime, docusate, dronabinol, esomeprazole, fluconazole, furosemide, glimepiride, human albumin, hydromorphone, insulin, insulin glargine, lidocaine, metformin, nadolol, omeprazole, ondansetron, oxycodone, salbutamol, senna alexandrina, sodium chloride, and sodium polystyrene sulfonate. At Screening, tumor assessments of target/non-target lesions via CT scan showed a lesion at the left liver lobe. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 14 Feb 2014 (Day 58), tumor response assessment showed disease progression and subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 13 Feb 2014 (Day 57).

On 28 Feb 2014 (Day 72), the subject was hospitalized for acute kidney injury (Grade 3) and also experienced leukocytosis (Grade 3), hypoalbuminemia (Grade 2), increased blood bilirubin (Grade 3), nausea (Grade 1), asthenia (Grade 3), dehydration (Grade 2), decreased weight (Grade 1) with weight of 75.75 kg (Baseline: 90.4 kg), abdominal distention (Grade 3) and peripheral edema (Grade 1). Laboratory tests showed WBC 13.4 x10^9/L (NR: 3.7 – 11), BUN 55.692 mmol/L (NR: 3.57 – 10.71), creatinine 442 umol/L (NR: 61.88 – 123.76), total bilirubin 124.83 umol/L (NR: 1.71 – 20.52), AST 276 U/L (NR: 1 – 50), ALT 63 U/L (NR: 1 – 53) and ALP 693 U/L (NR: 30 – 110). The subject was treated with sodium polystyrene sulfonate, human albumin, ondansetron, cefotaxime, sodium chloride, hydromorphone, and furosemide. The subject recovered from dehydration on 01 Mar 2014 (Day 73) and from hypoalbuminemia on 02 Mar 2014 (Day 74). On 03 Mar 2014 (Day 75), repeat laboratory tests showed BUN 3.3 mg/dL (NR: not provided) and creatinine 121 mg/dL (NR: not provided). The subject recovered from peripheral edema on 04 Mar 2014 (Day 76). On 10 Mar 2014 (Day 82, 25 days after the last dose), subject died due to disease progression. Autopsy was not performed. At the time of death, the subject had not recovered from acute kidney injury, nausea, asthenia, increased blood bilirubin, leukocytosis, decreased weight, and abdominal distention. The Investigator considered acute kidney injury serious and not related to study drug but related to disease progression; increased blood bilirubin nonserious and possibly

related to the study drug and related to disease progression; asthenia, decreased weight, abdominal distention, and peripheral edema nonserious and not related to study drug but related to disease progression; nausea nonserious and not related to the study drug but related to disease progression; leukocytosis and dehydration nonserious and not related to study drug.

Subject Number	12081021
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004222
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Tumour pain
AE(s) Leading to Discontinuation	Tumour pain
Death due to PD	Yes

An 82-year-old Japanese male was diagnosed with hepatocellular carcinoma on 26 Jan 2011. Significant medical history included chronic gastritis, hepatitis C, and hypertension. Previous anticancer therapies included high frequency ablation (2x) and transcatheter arterial chemoembolization (3x). Prior and concomitant medications included azilsartan, clobetasol, dextrose and sodium chloride injection, dimeticone, famotidine, flurbiprofen, glucose injection, indometacin, lidocaine, loxoprofen, magnesium oxide, new lecicarbon, nifedipine, oxycodone, paracetamol, pronase, rabeprazole, ringer-lactate, sennoside a+b, sodium bicarbonate, ultracet, urea, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left, right liver lobes, mesenteric and para-aortic lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 21 Nov 2014 (Day 1), treatment with study drug was initiated.

On 14 Dec 2014 (Day 24), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2). The subject was treated with clobetasol and urea. On 18 Dec 2014 (Day 28), the study drug dose was reduced to 400 mg/day due to this event. On 05 Jan 2015 (Day 46), the severity of palmar-plantar erythrodysesthesia syndrome improved to Grade 1 and on 15 Jan 2015 (Day 56), the subject recovered from this event. The Investigator considered this event nonserious and probably related to the study drug.

On 20 Jan 2015 (Day 61), the subject experienced tumor pain (Grade 1) in the abdomen. The study drug dose was not changed. On 12 Feb 2015 (Day 84), the severity of tumor pain worsened to Grade 2, and on the same day (Day 84) the study drug was interrupted. Laboratory tests showed CRP 74.3 mg/L (NR: 0 – 5), albumin 33 g/L (NR: 35 – 55), ALP 163 U/L (NR: 43 – 115), GGT 146 U/L (NR: 10 – 49), and AST 51 U/L (NR: 10 – 43). The subject was treated with famotidine, paracetamol, loxoprofen, and rabeprazole. On 17 Feb 2015 (Day 89), the subject was hospitalized for worsening of tumor pain (Grade 3). The subject also experienced acute kidney injury (Grade 1) and hypoalbuminemia (Grade 2). On the same day (Day 89), tumor response assessment showed disease progression and the subject was withdrawn from study drug due to tumor pain secondary to disease progression. Laboratory tests showed albumin 22 g/L (NR: 38 – 51), BUN 16.2435 mmol/L (NR: 2.856 – 7.497), and creatinine 163.54 umol/L (NR: 70.72 – 114.92). The subject was treated with flurbiprofen, paracetamol, ultracet, glucose injection, dextrose and sodium chloride injection, and ringer-lactate. The subject received the last dose of the study drug on 11 Feb 2015 (Day 83). On 20 Feb 2015 (Day 92), the severity of acute kidney injury worsened to Grade 3 and the subject also

experienced hyperkalemia (Grade 2). Laboratory tests showed CRP 165.3 mg/L, albumin 28 g/L (NR: 35 – 55), ALP 157 U/L, AST 38 U/L, GGT 114 U/L, BUN 23.56 mmol/L (NR: 1.78 – 7.14), creatinine 327 umol/L (NR: 62 – 124), potassium 5.9 mmol/L (NR: 3.7 – 4.9), and sodium 128 mmol/L (NR: 133 – 145). On 25 Feb 2015 (Day 97, 14 days after the last dose), the subject died due to disease progression. Autopsy was not performed. At the time of death, the subject did not recover from the tumor pain, acute kidney injury, hypoalbuminemia, and hyperkalemia. The Investigator considered tumor pain serious and not related to study drug but related to disease progression; acute kidney injury, hypoalbuminemia, and hyperkalemia nonserious and not related to the study drug but related to disease progression.

Section III Non-Fatal Serious Adverse Event

Arm: Lenvatinib

Subject Number	10031004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01566-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Urosepsis

A 66-year-old African American male was diagnosed with hepatocellular carcinoma on 05 Jul 2013. Significant medical history included abdominal discomfort, appendectomy, hematochezia, chronic kidney disease, diabetes mellitus, diabetic neuropathy, drug dependence, general pain, hemorrhoids, hepatitis C, hernia, hyperlipidemia, hypertension, joint dislocation (left patellar dislocation), nausea, strabismus, and vomiting. Previous anticancer therapies included high frequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included atenolol, bismuth, cefalexin, ceftriaxone, dicycloverine, gabapentin, gemfibrozil, hydromorphone, insulin aspart, meclozine, methadone, omeprazole, ondansetron, oxycocet, prochlorperazine, silybum marianum, sulfadiazine, and vitamins (multivitamins). At Screening, tumor assessments of target/non-target lesions via CT scan showed mass in lower and upper lobes of bilateral lungs; MRI showed left adrenal mass; lesions at left, caudate, right lobes, and segment 4 of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 25 Sep 2013 (Day 1), treatment with study drug was initiated.

On 23 Oct 2013 (Day 29), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 1). On 22 Nov 2013 (Day 59), palmar-plantar erythrodysesthesia syndrome worsened to Grade 2. On 22 Nov 2013 (Day 59), the study drug was interrupted due to the event and the subject was treated with sulfadiazine. On 27 Nov 2013 (Day 64), the severity of palmar-plantar erythrodysesthesia syndrome improved to Grade 1. On 09 Dec 2013 (Day 76), the subject recovered from this event and the study drug was resumed at a reduced dose of 8 mg/day due to this event. The Investigator considered palmar-plantar erythrodysesthesia syndrome nonserious and probably related to study drug.

On 25 Aug 2014 (Day 335), the study drug was interrupted due to pending tumor scan result. On 26 Aug 2014 (Day 336), tumor response assessment showed disease progression. On 27 Aug 2014 (Day 337), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 24 Aug 2014 (Day 334).

On 27 Aug 2014 (Day 337), the subject was hospitalized for urosepsis (Grade 3). The subject was found to be dehydrated and with a body temperature of 38.3 ºC. The subject also experienced asterixis (Grade 2), constipation (Grade 3), dysmetria (Grade 2), and amnesia (Grade 2). On 27 Aug 2014 (Day 337), blood culture showed no growth after 5 days, urine

culture was positive for E.coli, and WBC was 11.6 x10^9/L (NR: 3.7 – 11). The subject was treated with fluid replacement, ceftriaxone, and cefalexin. On 28 Aug 2014 (Day 338), head CT scan showed no evidence of stroke, bleeding, or metastatic lesions. On 01 Sep 2014 (Day 342), the subject recovered from urosepsis, asterixis, constipation, dysmetria, and amnesia. The subject was discharged from the hospital on the same day (Day 342). The Investigator considered urosepsis serious and not related to study drug; amnesia, asterixis, constipation, and dysmetria nonserious and not related to study drug.

On 20 Jun 2016 (Day 1000, 666 days after the last dose), the subject died due to disease progression.

Subject Number	10031011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000594
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Seizure

A 57-year-old white male was diagnosed with hepatocellular carcinoma on 09 Aug 2013. Significant medical history included head injury, hepatitis C, neck surgery, and decreased appetite. Previous anticancer therapies included high frequency ablation (2x) and transcatheter arterial chemoembolization. Prior and concomitant medications included antacids (maalox), dexamethasone, dronabinol, levetiracetam, lisinopril, omeprazole, oxycocet, and oxycodone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right portal vein; masses at right middle lobe of lung; bilateral hilar and subcarinal lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 09 Jul 2014 (Day 1), treatment with study drug was initiated.

On 17 Sep 2014 (Day 71), tumor response assessment showed disease progression. The MRI of brain showed additional new enhancing lesions scattered throughout the brain, suggestive of new metastases. On 19 Sep 2014 (Day 73), 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 73).

On 29 Sep 2014 (Day 83), the subject experienced seizure (Grade 1). On 30 Sep 2014 (Day 84), the subject was hospitalized for focal seizures without loss of consciousness. Treatment included levetiracetam and dexamethasone. On 01 Oct 2014 (Day 85), the subject recovered from seizure and was discharged from the hospital. The Investigator considered seizure serious (important medical event) and not related to study drug but related to disease progression.

On 02 Nov 2014 (Day 117, 44 days after the last dose), the subject died due to disease progression.

Subject Number	10031013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002656
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Clostridium test positive, Hyponatraemia, Nausea, Vomiting

A 70-year-old Asian male was diagnosed with hepatocellular carcinoma on 01 Jan 2014. Significant medical history included benign prostatic hyperplasia, carpal tunnel syndrome, constipation, coronary artery disease, diabetes mellitus, fatigue, gastroesophageal reflux disease, hepatitis C, hypertension, myocardial infarction, nausea, pain, portal vein thrombosis secondary to HCC invasion, papular rash, and vomiting. Previous anticancer therapy included y90 radioembolization. Prior and concomitant medications included acetylsalicylic acid, antiemetics and antinauseants, carvedilol, clotrimazole, docusate, esomeprazole, gelclair, glimepiride, hydromorphone, ibuprofen, lisinopril, magic mouthwash, metronidazole, ondansetron, paracetamol, and tamsulosin. At Screening, tumor assessments of target/non-target lesions via CT scan showed pancreatic, colorectal, periportal masses, and lymphadenopathy adjacent to inferior vena cava. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 22 Aug 2014 (Day 1), treatment with study drug was initiated.

On 18 Dec 2014 (Day 119), the subject was hospitalized for positive Clostridium difficile test (Grade 3). Stool culture confirmed Clostridium difficile toxin. On 19 Dec 2014 (Day 120), the study drug was interrupted due to this event and the subject was treated with intravenous solutions, metronidazole, and antiemetics and antinauseants (unspecified). On 21 Dec 2014 (Day 122), the subject recovered from the event and was discharged from the hospital. On 24 Dec 2014 (Day 125), the study drug was resumed at the same dose. The Investigator considered positive Clostridium difficile test serious and not related to the study drug.

On 02 Jan 2015 (Day 134), the subject was hospitalized for hyponatremia (Grade 3) with sodium 120 mmol/L (NR: 135 – 145) and also experienced constipation (Grade 2). On the same day (Day 134), the study drug was interrupted due to these events. Computed tomography scan of abdomen showed no evidence of small bowel obstruction. On 06 Jan 2015 (Day 138) the subject recovered from constipation and hyponatremia. The laboratory test showed sodium 132 mmol/L (NR: 133 – 145). The Investigator considered hyponatremia serious and possibly related to the study drug; constipation nonserious and possibly related to the study drug.

On 09 Jan 2015 (Day 141), the subject was withdrawn from the study due to the clinical disease progression and received the last dose of the study drug on 01 Jan 2015 (Day 133). Laboratory tests showed AFP 4168.7 ug/L (NR: 0 – 6.1; Screening: 2314.9 ug/L).

On 20 Jan 2015 (Day 152), the subject was hospitalized for nausea (Grade 2) and vomiting (Grade 2). The subject also experienced abdominal pain (Grade 2) and lower back pain (Grade 2). Laboratory tests showed sodium 128 mmol/L (NR: 135 – 145) and

potassium 4.1 mmol/L (NR: 3.5 – 5). The subject was treated with ondansetron. On 26 Jan 2015 (Day 158), the subject recovered from all the events and was discharged from the hospital. The Investigator considered nausea, vomiting serious and not related to the study drug; abdominal pain, lower back pain nonserious and not related to study drug.

On 06 Feb 2015 (Day 169), tumor response assessment showed disease progression.

On 21 Mar 2015 (Day 212, 79 days after the last dose), the subject died due to disease progression.

Subject Number	10061007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002771
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Ascites, Peripheral swelling

A 57-year-old white male was diagnosed with hepatocellular carcinoma on 08 Sep 2014. Significant medical history included alcohol abuse, appendectomy, hepatic cirrhosis, cough, deep vein thrombosis right leg, peripheral edema (edema in legs), non-bleeding esophageal varices, esophagitis, fatigue, hepatitis C, drug abuse, muscle spasms, abdominal pain upper (left), night sweats, portal hypertension, and tobacco user (smoking cigarettes). The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, amlodipine, amoxicillin, benicar hct, cefalexin, clotrimazole, furosemide, nadolol, omeprazole, ondansetron, oxycodone, prochlorperazine, salbutamol, solpadeine, spironolactone, vancomycin, vicks formula, and vitamins (multivitamins). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes; para-aortic, pericardiophrenic, and prevascular space lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 17 Oct 2014 (Day 1), treatment with study drug was initiated.

On 14 Nov 2014 (Day 29), the subject experienced peripheral swelling (right leg; Grade 3) which started on 07 Oct 2014 (Day –10) as Grade 1. The study drug was interrupted due to this event and the subject was treated with cefalexin and solpadeine. On 17 Nov 2014 (Day 32), the subject had ultrasound of leg. On 18 Nov 2014 (Day 33), the subject was hospitalized for ascites (Grade 3) and persistent peripheral swelling. The subject also experienced dyspnea (Grade 1) on the same day (Day 33). The study drug remained interrupted due to ascites. Treatment included acetylsalicylic acid, furosemide, salbutamol, spironolactone, vancomycin, and oxycodone. On 19 Nov 2014 (Day 34), abdominal ultrasound and CT scan of abdomen and pelvis confirmed ascites. On 21 Nov 2014 (Day 36), the subject underwent abdominal paracentesis and a venogram of the right leg showed no mechanical obstruction. On same day (Day 36), the subject recovered from ascites, dyspnea and was discharged from the hospital. The subject did not recover from peripheral swelling. The Investigator considered ascites and peripheral swelling serious and not related to study drug; dyspnea nonserious and not related to study drug.

On 12 Dec 2014 (Day 57), the subject was withdrawn from the study due to subject's choice and received the last dose of the study drug on 13 Nov 2014 (Day 28).

On 17 Mar 2015 (Day 152, 124 days after the last dose), the subject died due to unknown cause.

Subject Number	10061014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010148
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Sepsis

A 62-year-old white male was diagnosed with hepatocellular carcinoma on 29 Apr 2013. Significant medical history included alcohol use, anxiety, arthralgia (chronic knee pain), chronic insomnia, hepatic cirrhosis, depression, dyshidrotic eczema, eosinophilia, erectile dysfunction, cholecystectomy, hepatitis C, drug abuse, asthma, hemorrhoids, portal hypertension, ankle operation, shoulder operation, right knee fracture, tobacco user, and hypertension. Previous anticancer therapies included microwave therapy, high frequency ablation, and transcatheter arterial chemoembolization (5x). Prior and concomitant medications included amidotrizoic acid, antacids (gaviscon), augmentin, bactrim, bismuth, budesonide w/formoterol fumarate, ciprofloxacin, docusate, hydrocortisone, hydromorphone, loperamide, loratadine, menthol w/methyl salicylate, ocuvite, oxycodone, piperacillin/tazobactam, rifaximin, salbutamol, senna alexandrina, serenoa repens, seretide, sodium chloride, tramadol, vancomycin, vicodin, vitamins, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right, left, and caudate lobes of liver, mass at right upper lobe lung, and left mediastinal lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 30 Apr 2015 (Day 1), treatment with study drug was initiated.

On 14 May 2015 (Day 15), the subject experienced increased blood alkaline phosphatase (Grade 3) with ALP 628 U/L (NR: 43 – 115) and increased aspartate aminotransferase (Grade 3) with AST 220 U/L (NR: 10 – 43). On 28 May 2015 (Day 29), the severity of increased aspartate aminotransferase and increased blood alkaline phosphatase improved to Grade 2, and the subject also experienced increased blood bilirubin (Grade 1). Laboratory tests showed AST 189 U/L, ALT 149 U/L (NR: 10 – 40), albumin 31 g/L (NR: 35 – 55), ALP 559 U/L, and total bilirubin 44.6 umol/L (NR: 0 – 18.8). On the following day (Day 30), the study drug was interrupted due to these events. On 04 Jun 2015 (Day 36), the severity of increased aspartate aminotransferase improved to Grade 1 and severity of increased blood bilirubin worsened to Grade 2. The subject was recovering from increased aspartate aminotransferase, increased blood alkaline phosphatase and did not recover from increased blood bilirubin. On 08 Jun 2015 (Day 40), the study drug was resumed at a reduced dose of 8 mg/day due to increased blood alkaline phosphatase and increased aspartate aminotransferase. The Investigator considered increased aspartate aminotransferase, increased blood alkaline phosphatase, and increased blood bilirubin nonserious and not related to the study drug.

On 25 Jun 2015 (Day 57), the subject experienced jaundice (Grade 2). Laboratory tests showed total bilirubin 59.5 umol/L, albumin 31 g/L, ALT 127 U/L, and AST 161 U/L. On 26 Jun 2015 (Day 58), the study drug was interrupted due to jaundice and ongoing increased blood bilirubin. On 24 Jul 2015 (Day 86), the study drug was resumed at the same dose. On 06 Aug 2015

(Day 99), the subject had endoscopic retrograde cholangiopancreatography, which showed obstruction at hepatic bifurcation and inability to pass wire into left hepatic duct, and underwent plastic stent placement. On 15 Aug 2015 (Day 108), the severity of increased blood bilirubin worsened to Grade 3 with total bilirubin 186.39 umol/L (NR: 0 – 20.52). On 17 Aug 2015 (Day 110), the study drug was interrupted due to increased blood bilirubin. On 20 Aug 2015 (Day 113), the severity of increased blood bilirubin worsened to Grade 4 with total bilirubin 263.9 umol/L (NR: 0 – 18.8). On 26 Aug 2015 (Day 119), the subject underwent percutaneous transhepatic biliary drainage and stent replacement. The subject did not recover from jaundice and increased blood bilirubin. The Investigator considered increased blood bilirubin and jaundice nonserious and not related to the study drug.

On 29 Aug 2015 (Day 122), the subject experienced abdominal wall infection (Grade 3) and medical device site abscess (Grade 2). On the same day (Day 122), the subject was hospitalized for sepsis (sepsis related to stent abscess and abdominal wall infection; Grade 4). Blood cultures were positive for gram-negative rods. The study drug remained interrupted due to sepsis. Laboratory tests showed total bilirubin 256.5 umol/L (NR: 0 – 20.52), differential neutrophils 77% (NR: 40 – 74), and WBC 9.1 x10^9/L (NR: 3.4 – 10.8). The CT scan of abdomen and pelvis showed lobular low density collection in the porta hepatis possibly fluid collection or abscess; cirrhotic liver with multiple low density mass lesions compatible with cirrhosis and hepatoma, diffuse small bowel mucosal thickening, and throughout the large bowel small volume of ascites, diffuse mesenteric edema, gastrohepatic ligament, and periportal adenopathy. The subject was treated with ciprofloxacin, augmentin, oxycodone, bactrim, piperacillin/tazobactam, vancomycin, and sodium chloride. On 03 Sep 2015 (Day 127), the subject experienced bile duct obstruction (Grade 3) which was confirmed via endoscopic retrograde cholangiopancreatography. On 05 Sep 2015 (Day 129), the subject recovered from sepsis and was discharged from the hospital. The subject did not recover from bile duct obstruction, abdominal wall infection, and medical device site abscess. The Investigator considered sepsis serious and not related to the study drug; bile duct obstruction, abdominal wall infection, and medical device site abscess nonserious and not related to study drug.

On 11 Sep 2015 (Day 135), the subject was withdrawn from study due to clinical disease progression and received the last dose of the study drug on 16 Aug 2015 (Day 109).

On 13 Oct 2015 (Day 167, 58 days after the last dose), the subject died due to unknown cause.

Subject Number	10071012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004802
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy

A 64-year-old African American male was diagnosed with hepatocellular carcinoma in Jul 2013. Significant medical history included abdominal pain, drug hypersensitivity (allergy to tamsulosin), bacterial pneumonia, benign prostatic hyperplasia, bradycardia, chronic back pain, chronic hepatitis C, chronic obstructive pulmonary disease, bone pain (clavicle pain-intermittent per patient), contact dermatitis, deep vein thrombosis, chronic cardiac failure (diastolic heart failure, NYHA Class I), dysphagia, eczema, gastroesophageal reflux disease, fatigue, glucose tolerance impaired, guttate psoriasis, congenital neuropathy (hereditary and idiopathic peripheral neuropathy), hyperlipidemia, hypertension, toxic neuropathy, arthralgia (joint pain - multiple sites), pulmonary mass, obesity, osteomyelitis, peripheral arterial occlusive disease, rash and other nonspecific skin eruption, schizophrenia, sleep apnea syndrome, thrombocytopenia, and tinea cruris. Previous anticancer therapy included high frequency ablation. Prior and concomitant medications included acetylsalicylic acid, amlodipine, atorvastatin, beclometasone, betamethasone, calcipotriol, capsaicin, cefepime, clindamycin, clobetasol, clopidogrel, fluticasone, furosemide, hydroxyzine, lactulose, lidocaine, methadone, midazolam, omeprazole, oxycodone, pethidine, potassium, pregabalin, promethazine, ranitidine, salbutamol, seretide, tazarotene, tiotropium, and vancomycin. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass at the upper lobe of right lung and MRI showed lesion at the right liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 02 Mar 2015 (Day 4), the subject experienced mental status changes (Grade 3). On 03 Mar 2015 (Day 5), the subject was hospitalized for hepatic encephalopathy (Grade 3) and also experienced somnolence (Grade 3). On 03 Mar 2015 (Day 5), the study drug was interrupted due to these events. On 04 Mar 2015 (Day 6), the subject experienced confusional state (Grade 2), leukocytosis (Grade 3), and pyrexia (Grade 1) with body temperature of 37.7 ºC. Laboratory tests showed AST 449 U/L (NR: 15 – 43), ALT 118 U/L (NR: 6 – 63), ALP 200 U/L (NR: 35 – 115), total bilirubin 32.49 umol/L (NR: 5.13 – 22.23), WBC 12.2 x10^9/L (NR: 4.5 – 11), and ammonia 28 umol/L (NR: 2 – 30). Treatment included cefepime, lactulose, and vancomycin. On 05 Mar 2015 (Day 7), the subject recovered from pyrexia. On 06 Mar 2015 (Day 8), the subject experienced portal vein thrombosis (Grade 2) and hyperammonemia (Grade 2) with ammonia 66 umol/L. On 07 Mar 2015 (Day 9), the subject recovered from leukocytosis with repeat WBC 9.3 x10^9/L. On 11 Mar 2015 (Day 13), the subject recovered from hepatic encephalopathy. The subject did not recover from mental status changes, somnolence, confusional state, hyperammonemia, and portal vein thrombosis. The Investigator considered hepatic encephalopathy serious and not related to study drug but related to clinical disease progression; portal vein thrombosis nonserious and not related to study drug

but related to clinical disease progression; somnolence nonserious and possibly related to study drug; pyrexia, leukocytosis, mental status changes, confusional state, and hyperammonemia nonserious and not related to study drug.

On 02 Apr 2015 (Day 35), the subject withdrew consent from participating in the study and received the last dose of the study drug on 02 Mar 2015 (Day 4).

Subject Number	10091004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01505-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hydrocholecystis, Hepatic encephalopathy (4x), Urinary tract infection (2x), Dehydration, Confusional state

A 66-year-old white female was diagnosed with hepatocellular carcinoma on 15 Jan 2014. Significant medical history included alcohol use, asthma, chronic vaginal infection, tinnitus, type 2 diabetes mellitus, ammonia increased, increased blood cholesterol, urinary tract infections, hepatic encephalopathy, hypertension, hypothyroidism, arthralgia, arthralgia (left forearm joint pain), musculoskeletal pain (left shoulder pain), hepatic cirrhosis, non-alcoholic steatohepatitis, sleep apnea syndrome, osteoporosis, urinary incontinence, and vertigo. Previous anticancer therapy included radiotherapy to mass in the right lobe of liver. Prior and concomitant medications included acetylsalicylic acid, aludrox, azithromycin, bactrim, calcium, cefalexin, cefazolin, ceftriaxone, ciprofloxacin, cyclobenzaprine, daptomycin, diltiazem, doxycycline, el-4, enoxaparin, estradiol, famotidine, fluconazole, furosemide, gabapentin, glimepiride, hydrocodone, hydromorphone, ibuprofen, influenza vaccine, insulin aspart, insulin detemir, insulin glargine, insulin lispro, lactulose, levofloxacin, levothyroxine, magic mouthwash, magnesium, meclozine, menthol, metformin, methylprednisolone, metoclopramide, neotracin, nitrofurantoin, nystatin, ondansetron, oseltamivir, osmotan, paracetamol, phenazopyridine, polymyxin B w/trimethoprim, prednisolone, prednisone, rifaximin, simvastatin, sodium chloride, spironolactone, sulfamethoxazole, tocopherol, tramadol, vaccinium macrocarpon, vicodin, and vitamins. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions in the left and right lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 19 Mar 2014 (Day 1), treatment with study drug was initiated.

On 07 May 2014 (Day 50), the subject experienced hydrocholecystis (Grade 2). An MRI of abdomen and pelvis showed hydropic gallbladder and some layering of pigmented bile salts or sludge within the gallbladder. On 14 May 2014 (Day 57), the study drug was interrupted due to the event. On the same day (Day 57), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2). On 19 May 2014 (Day 62), the subject was hospitalized for hydrocholecystis (Grade 3) and underwent laparoscopic cholecystectomy. Later that day (Day 62), the subject experienced incision site pain (Grade 2). Treatment included aludrox, cefazolin, el-4, famotidine, hydromorphone, metoclopramide, ondansetron, and vicodin. On 20 May 2014 (Day 63), the subject recovered from hydrocholecystis. On 04 Jun 2014 (Day 78), the subject recovered from incision site pain, palmar-plantar erythrodysesthesia syndrome and the study drug was resumed at a reduced dose of 8 mg/day due to palmar-plantar erythrodysesthesia syndrome. The Investigator considered hydrocholecystis serious and not related to study drug; palmar-plantar erythrodysesthesia syndrome nonserious and probably related to study drug; incision site pain nonserious and not related to study drug.

On 22 Jul 2014 (Day 126), the subject experienced altered mental status, confusion, and was hospitalized with a diagnosis of hepatic encephalopathy (Grade 3). The study drug was interrupted due to the event. Laboratory tests showed AST 41 U/L (NR: 15 – 46), ALT 45 U/L (NR: 14 – 69), ALP 153 U/L (NR: 38 – 126), total bilirubin 27.36 umol/L (NR: 3.42 – 22.23), and ammonia 22 umol/L (NR: 9 – 30). The subject was observed and no other treatment was provided. On 23 Jul 2014 (Day 127), the subject recovered and was discharged from the hospital. On 24 Jul 2014 (Day 128), the study drug was resumed at the same dose. The Investigator considered hepatic encephalopathy serious and not related to the study drug.

On 27 Aug 2014 (Day 162), the subject experienced persistent pain in extremity (Grade 3) which started as Grade 1 on 16 Jul 2014 (Day 120) and the study drug was interrupted due to the event. On 08 Sep 2014 (Day 174), the study drug was resumed at reduced dose of 4 mg/day due to pain in extremity. On 09 Sep 2014 (Day 175), pain in extremity improved to Grade 1. On 24 Sep 2014 (Day 190), the subject recovered from the event. The Investigator considered pain in extremity nonserious and probably related to study drug.

On 23 Oct 2014 (Day 219), the subject experienced urinary tract infection (Grade 2) and was treated with doxycycline. On 19 Dec 2014 (Day 276), the subject was hospitalized for urinary tract infection (Grade 3) and hepatic encephalopathy (Grade 3) with symptoms of confusion and altered mental status. On the same day (Day 276), CT scan of brain showed no acute changes. Laboratory tests showed ALT 41 U/L (NR: 12 – 78), AST 36 U/L (NR: 10 – 45), ALP 288 U/L (NR: 45 – 132), total bilirubin 23.94 umol/L (NR: 0 – 17.1), and ammonia 18 umol/L (NR: 3 – 37). Urine dipstick showed protein 1+, leukocytes 3+, and blood 3+. The subject was treated with levofloxacin. On 20 Dec 2014 (Day 277), the subject recovered with sequelae from hepatic encephalopathy and urinary tract infection. The Investigator considered hepatic encephalopathy and urinary tract infection serious and not related to study drug.

On 01 Jan 2015 (Day 289), the subject was hospitalized for hepatic encephalopathy (Grade 3), Enterococcal urinary tract infection (Grade 3), and dehydration (Grade 2). She also had hyponatremia (Grade 1) and mental status changes (Grade 2). Laboratory tests showed sodium 130 mmol/L (NR: 137 – 145), AST 57 U/L (NR: 15 – 46), ALT 39 U/L (NR: 14 – 69), ALP 212 U/L (NR: 38 – 126), total bilirubin 30.78 umol/L (NR: 3.42 – 22.23), and ammonia 9 umol/L (NR: 9 – 30). Urine culture grew Enterococci. Treatment included nitrofurantoin and sodium chloride. On 05 Jan 2015 (Day 293), the subject recovered from dehydration, hepatic encephalopathy, mental status changes, and was discharged from the hospital. On 06 Jan 2015 (Day 294), Enterococcal urinary tract infection improved to Grade 2. On 14 Jan 2015 (Day 302), the subject recovered from hyponatremia with sodium 136 mmol/L (NR: 133 – 145). On 07 Mar 2015 (Day 354), the subject underwent bladder biopsy due to frequent urinary tract infections (result not provided). On 08 Mar 2016 (Day 721), the subject recovered from Enterococcal urinary tract infection. The Investigator considered dehydration, hepatic encephalopathy, Enterococcal urinary tract infection serious and not related to study drug; mental status changes and hyponatremia nonserious and not related to study drug.

On 21 Jan 2015 (Day 309), the subject was hospitalized for confusional state (Grade 3) and also had dehydration (Grade 2). The subject was treated with sodium chloride and osmotan. On 28 Jan 2015 (Day 316), the subject recovered with sequelae from confusional state; recovered from dehydration and was discharged from hospital. The Investigator considered confusional state serious and not related to study drug; dehydration nonserious and not related to study drug.

On 15 Jun 2016 (Day 820), the subject was hospitalized for hepatic encephalopathy (Grade 3). The subject did not receive any treatment. On 17 Jun 2016 (Day 822), the subject recovered from this event. The Investigator considered hepatic encephalopathy serious and not related to study drug.

On 06 Jul 2016 (Day 841), the subject experienced decreased appetite (Grade 2). The study drug was interrupted due to the event. On 17 Aug 2016 (Day 883), the subject recovered from the event. The Investigator considered decreased appetite nonserious and possibly related to the study drug.

On 14 Sep 2016 (Day 911), the subject withdrew from the study by choice and received the last dose of the study drug on 05 Jul 2016 (Day 840).

Subject Number	10121003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011714
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Posterior reversible encephalopathy syndrome

A 74-year-old white male was diagnosed with hepatocellular carcinoma on 13 Mar 2009. Significant medical history included abdominal pain, back pain, hepatic cirrhosis, peripheral edema, fatigue, hepatitis C, peripheral vascular disorder, and fibroma (soft fibroma left leg). Previous anticancer therapies included percutaneous ethanol injection therapy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included furosemide, hydromorphone, metoprolol, and morphine. At Screening, tumor assessments of target/non-target lesions via MRI showed lesion at left and right lobes of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 20 Feb 2014 (Day 1), treatment with study drug was initiated.

On 20 Feb 2014 (Day 1), the subject experienced posterior reversible encephalopathy syndrome (Grade 2) with symptom of increased confusion, worsening balance, poor memory, and blurred vision. The subject had a blood pressure of 120/68 mmHg and 154/81 mmHg. The subject also experienced nausea (Grade 2), hypoesthesia (Grade 1), anorexia (Grade 2), and dysphonia (Grade 1). The subject was clinically diagnosed and no imaging was performed to confirm posterior reversible encephalopathy syndrome. On 06 Mar 2014 (Day 15), the subject experienced hypertension (Grade 3) with BP of 167/109 mmHg. Treatment included metoprolol and the study drug was interrupted due to posterior reversible encephalopathy syndrome and hypertension. The subject recovered from dysphonia. On 13 Mar 2014 (Day 22), the subject recovered with sequelae from posterior reversible encephalopathy syndrome and recovered from hypertension with BP of 112/56 mmHg. The subject did not recover from anorexia, hypoesthesia, and nausea. The Investigator considered posterior reversible encephalopathy syndrome serious (important medical event) and probably related to study drug; hypertension, anorexia, dysphonia, and nausea nonserious and probably related to study drug; hypoesthesia nonserious and not related to study drug.

On 19 Mar 2014 (Day 28), the subject withdrew consent from the study and received the last dose of the study drug on 06 Mar 2014 (Day 15).

On 27 Apr 2014 (Day 67, 52 days after the last dose), the subject died due to disease progression.

Subject Number	10141001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01437-CLI-US
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diverticulitis

An 81-year-old white female was diagnosed with hepatocellular carcinoma on 21 Jan 2013. Significant medical history included allergic rhinitis, anxiety, carpal tunnel decompression, cataract operation (both eyes), cholecystectomy, large intestine polyp, dermatitis, diverticulum, exertional dyspnea, erosive gastritis, fatigue, impaired gastric emptying, gastroesophageal reflux disease, gout, hyperlipidemia, hypertension, hypothyroidism, knee arthroplasty, rubber sensitivity, lower back pain, spinal osteoarthritis, obesity, peripheral edema, portal hypertensive gastropathy, motion sickness, non-alcoholic fatty liver, hysterectomy (partial), portal hypertension, postmenopause, tachycardia, type 2 diabetes mellitus, and vertigo. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included allopurinol, diltiazem, diovan amlo, domperidone, hydrochlorothiazide, insulin glargine, levothyroxine, meclozine, metformin, metoprolol, metronidazole, omeprazole, promethazine, unacid, and vicodin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at segment 6 of the left lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 02 Dec 2013 (Day 1), treatment with study drug was initiated.

On 17 Dec 2013 (Day 16), the subject was hospitalized for diverticulitis (Grade 3) with symptoms of diarrhea, severe vomiting, and mild abdominal tenderness to the left lower quadrant area. The CT scan of abdomen and pelvis showed focal diverticulitis involving sigmoid colon. The study drug dose did not change. The subject was treated with unacid and metronidazole. On 18 Dec 2013 (Day 17), the subject recovered from diverticulitis and was discharged from the hospital. The Investigator considered diverticulitis serious and not related to study drug.

On 30 Dec 2013 (Day 29), the subject withdrew from the study by choice and received the last dose of study drug on 26 Dec 2013 (Day 25).

Subject Number	10151002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01440-CLI-US
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Suicide attempt, Major depression, Intentional overdose, Syncope (2x), Muscular weakness, Myocardial infarction
AE(s) Leading to Discontinuation	Myocardial infarction

A 76-year-old Chinese male was diagnosed with hepatocellular carcinoma on 11 June 2013. Significant medical history included decreased appetite, back pain, benign prostatic hyperplasia, spinal osteoarthritis, depression, hepatitis C, hypertension, insomnia, spinal laminectomy, upper abdominal pain (right upper quadrant), partial gastrectomy, peripheral sensory neuropathy, arthralgia (right hip pain), and muscular weakness (right leg). Previous anticancer therapies included radiotherapy to sternum and vertebral (T10 – L5) lesion and transcatheter arterial chemoembolization. Prior and concomitant medications included acetylsalicylic acid, amlodipine, atorvastatin, carvedilol, cefazolin, ceftriaxone, celecoxib, ciprofloxacin, clonidine, clopidogrel, cyclobenzaprine, digoxin, dopamine, dutasteride, enalapril, fentanyl, furosemide, gabapentin, glyceryl trinitrate, hydromorphone, influenza vaccine, iron, ketorolac, lidocaine, lisinopril, lorazepam, metoprolol, midazolam, morphine, naloxone, olmesartan, oxycocet, oxycodone, pantoprazole, paracetamol, pneumococcal vaccine, prednisone, pregabalin, quetiapine, ranolazine, tamsulosin, temazepam, ticagrelor, vancomycin, venlafaxine, vicodin, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at the right hepatic dome, lumbar vertebral masses at L1 – L4 and T5. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 24 Jan 2014 (Day 38), the subject was hospitalized for suicide attempt (Grade 4), intentional overdose (intentional overdose of oxycontin; Grade 4), and major depression (Grade 4). The subject also had respiratory depression (Grade 3). Urine drug screen was positive for barbiturates, benzodiazepines, and opiates. The subject was treated with naloxone and venlafaxine. The study drug was interrupted due to suicide attempt, intentional overdose, and major depression. On 26 Jan 2014 (Day 40), the subject recovered from respiratory depression. On 04 Feb 2014 (Day 49), the subject recovered from intentional overdose, suicide attempt, and major depression. On the same day (Day 49), the study drug was resumed at the same dose. The Investigator considered suicide attempt, intentional overdose, and major depression serious and not related to the study drug; respiratory depression nonserious and not related to the study drug.

On 17 Apr 2014 (Day 121), the subject was hospitalized for syncope (Grade 3), and also experienced a fall (Grade 2) which resulted to a rib fracture (Grade 2). Brain CT scan was negative; x-ray and CT scan of chest showed right rib fracture of the 9th rib, and laboratory tests were not considered clinically significant. On the same day (Day 121), the subject recovered

from fall, syncope, and recovered from rib fracture on 02 Jun 2014 (Day 167). The Investigator considered syncope serious and not related to the study drug; fall and rib fracture nonserious and not related to the study drug.

On 05 Oct 2014 (Day 292), the subject was hospitalized for muscular weakness (weakness of left upper extremity; Grade 3). On 06 Oct 2014 (Day 293), the study drug was interrupted. Bilateral duplex carotid ultrasound was not clinically significant and x-ray of the limb and brain MRI revealed normal findings. On 09 Oct 2014 (Day 296), the study drug was resumed at the same dose. The subject did not recover from muscular weakness. The Investigator considered muscular weakness serious and not related to the study drug.

On 30 Nov 2014 (Day 348), the subject was hospitalized for myocardial infarction (Grade 3) and coronary angiogram showed severe left main disease and triple vessel coronary disease. The subject underwent left heart cardiac catheterization, percutaneous coronary intervention of the right coronary artery, left main, and circumflex artery with stenting of the left main artery which resulted in reduction of stenosis. The subject was also treated with digoxin, glyceryl trinitrate, acetylsalicylic acid, atorvastatin, ranolazine, ticagrelor, dopamine, clopidogrel, and the study drug was withdrawn due to myocardial infarction. The subject received the last dose of the study drug on 30 Nov 2014 (Day 348). On 04 Dec 2014 (Day 352), the subject was discharged from hospital. However, on 05 Dec 2014 (Day 353), the subject fell due to syncope (Grade 3) and was hospitalized again. The subject was treated with unspecified medications and antibiotics. Laboratory tests and echocardiogram were not clinically significant. On 05 Dec 2014 (Day 353), the severity of myocardial infarction improved to Grade 2 and the subject recovered from syncope. On 11 Dec 2014 (Day 359), the subject recovered from myocardial infarction. On 17 Dec 2014 (Day 365), the subject was withdrawn from the study due to myocardial infarction. The Investigator considered myocardial infarction serious and possibly related to the study drug; syncope serious and not related to the study drug.

On 22 Jan 2015 (Day 401, 53 days after the last dose), the subject died due to disease progression.

Subject Number	10151006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01502-CLI-US
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Hyponatraemia, Fall, Thoracic vertebral fracture

A 66-year-old Chinese female was diagnosed with hepatocellular carcinoma on 27 Dec 2012. Significant medical history included abdominal pain, drug hypersensitivity (sulfa, bactrim, clindamycin, penicillin, and amoxicillin), anemia, arthralgia (ankle joint), ascites, asthma, large intestine polyp, cholelithiasis, chronic hepatitis B, hepatic cirrhosis, diabetes mellitus, epistaxis, esophageal varices, gastroesophageal reflux disease, granuloma, hemorrhoids, hyperbilirubinemia, hypercholesterolemia, hypertension, ileus, decreased blood potassium, amnesia, nausea, portal hypertension, lung disorder, splenomegaly, seborrheic keratosis, thrombocytopenia, and fluid retention. Previous anticancer therapies included transcatheter arterial chemoembolization. Prior and concomitant medications included bisacodyl, bismuth, calcium carbonate, docusate, entecavir, furosemide, ibuprofen, insulin glargine, lisinopril, macrogol, metformin, movicol, ondansetron, oxycodone, pantoprazole, potassium, procet, prochlorperazine, sodium chloride, spironolactone, tenofovir, and xantofyl. At Screening, tumor assessments of target/non-target lesions via CT showed lesions at quadrate lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 7.

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

On 16 May 2014 (Day 44), the subject was hospitalized for hyponatremia (Grade 4) with sodium 119 mmol/L (NR: 133 – 145) which started on 20 Mar 2014 (Day –14) as Grade 3. On 17 May 2014 (Day 45), the study drug was interrupted due to hyponatremia. The subject was treated with intravenous sodium chloride. On 29 May 2014 (Day 57), the study drug was resumed at the same dose. The subject did not recover from the event. The Investigator considered hyponatremia serious and not related to the study drug.

On 05 Sep 2014 (Day 156), the subject experienced a fall (mechanical fall; Grade 3) down flight of stairs at home which resulted in thoracic vertebral fracture (fracture T6 injury; Grade 3). Computerized tomography of thorax showed T6 compression fracture along with some rib contusions. The subject was hospitalized for fall and thoracic vertebral fracture. The subject was treated with oxycodone and the study drug dose did not change. The subject recovered from fall on the same day (Day 156). On 08 Sep 2014 (Day 159), the subject was discharged from the hospital to the nursing home. On 12 Sep 2014 (Day 163), the study drug was interrupted due to thoracic vertebral fracture. On 28 Oct 2014 (Day 209), the subject recovered from thoracic vertebral fracture. The Investigator considered fall and thoracic vertebral fracture serious and not related to the study drug.

On 08 Oct 2014 (Day 189), tumor response assessment showed disease progression. On 28 Oct 2014 (Day 209), the subject was withdrawn from the study due to disease progression and received the last dose on 11 Sep 2014 (Day 162).

On 09 Apr 2015 (Day 372, 210 days after the last dose), the subject died due to disease progression.

Subject Number	12011002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01443-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Perihepatic abscess, Infected neoplasm

A 69-year-old Japanese male was diagnosed with hepatocellular carcinoma on 18 Dec 2009. Significant medical history included chronic hepatitis B. Previous anticancer therapies included hepatectomy (2x), percutaneous ethanol injection, high frequency ablation (4x), and transcatheter arterial chemoembolization (3x). Prior and concomitant medications included carbazochrome, ceftriaxone, clobetasol, dextromethorphan, diclofenac, difluprednate, dimeticone, entecavir, flurbiprofen, glycerol, heparinoid, hydroxyzine, indigo carmine, lac-b granular powder n, levofloxacin, lidocaine, paracetamol, pentazocine, pronase, pyridoxal, riboflavin, sodium bicarbonate, sorbit hartman, stomatologicals, mouth preparations, and sulperazon. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver and peritoneal omental mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 21 Jan 2014 (Day 1), treatment with study drug was initiated.

On 04 Feb 2014 (Day 15), subject was hospitalized for perihepatic abscess (Grade 3) and also experienced palmar-plantar erythrodysesthesia syndrome (Grade 1). The CT scan of the abdomen showed fluid accumulation around the radiofrequency ablation (RFA) site and bile leakage from RFA site. The subject underwent liver abscess drainage and was treated with paracetamol, levofloxacin, hydroxyzine, carbazochrome, sorbit hartman, pentazocine, flurbiprofen, sulperazon, diclofenac, and ceftriaxone. On 10 Feb 2014 (Day 21), the severity of perihepatic abscess improved to Grade 2 and on 12 Feb 2014 (Day 23), the severity of palmar-plantar erythrodysesthesia syndrome worsened to Grade 3. On 13 Feb 2014 (Day 24), the study drug was interrupted due to palmar-plantar erythrodysesthesia syndrome. The subject was treated with difluprednate, riboflavin, pyridoxal, and clobetasol. On 14 Feb 2014 (Day 25), the perihepatic abscess improved to Grade 1. On 17 Feb 2014 (Day 28), the subject recovered from perihepatic abscess. On 25 Feb 2014 (Day 36), the palmar-plantar erythrodysesthesia syndrome improved to Grade 1. On the same day (Day 36), study drug was resumed at reduced dose of 4 mg/day due to palmar-plantar erythrodysesthesia syndrome. On 19 May 2014 (Day 119), the subject recovered from palmar-plantar erythrodysesthesia syndrome. The Investigator considered perihepatic abscess serious and not related to the study drug; palmar-plantar erythrodysesthesia syndrome nonserious and probably related to the study drug.

On 13 Mar 2014 (Day 52), the subject again experienced perihepatic abscess (Grade 1). On 08 May 2014 (Day 108), tumor response assessment showed disease progression. On 13 May 2014 (Day 113), the subject was withdrawn from the study due to disease progression and the subject received the last dose of study drug on the same day (Day 113). On 16 May 2014 (Day 116), the severity of perihepatic abscess worsened to Grade 2.