Subject Number	18071001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004440
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Blood bilirubin increased
AE(s) Leading to Discontinuation	Blood bilirubin increased

A 64-year-old white male was diagnosed with hepatocellular carcinoma on 23 Jan 2014. Significant medical history included congenital coagulopathy, esophageal varices, hypertension, spinal pain, hemorrhoids, eczema, rosacea, hepatic cirrhosis, and non-alcoholic steatohepatitis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included blopress plus, furosemide, lactulose, lercanidipine, levothyroxine, metoclopramide, metronidazole, pancreatin, pantoprazole, povidone-iodine, propranolol, rifaximin, sodium chloride, spironolactone, torasemide, ursodeoxycholic acid, and xylometazoline. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

On 27 Feb 2014 (Day 1), treatment with study drug was initiated.

On 09 Oct 2014 (Day 225), the subject experienced increased blood bilirubin (Grade 3). See table below. The study drug was interrupted due to increased blood bilirubin. On 16 Oct 2014 (Day 232), severity of increased blood bilirubin improved to Grade 2. On 22 Oct 2014 (Day 238), the study drug was resumed at same dose. The subject did not recover from this event. The Investigator considered the event nonserious and possibly related to the study drug.

On 26 Feb 2015 (Day 365), the subject was hospitalized for worsening of increased blood bilirubin (Grade 3). See table below. The subject also experienced hepatic encephalopathy (Grade 1) with ammonia levels 82.5 umol/L (NR: 0 – 50), somnolence (Grade 1), and jaundice (Grade 3). On the same day (Day 365), prior to admission, the subject also experienced a fall on his head (Grade 1) at home with no loss of consciousness, sustaining wound hematoma (head; Grade 1). The subject also experienced dizziness (Grade 2), fatigue (Grade 2), and malaise (Grade 2). The study drug was interrupted due to increased blood bilirubin. Treatment included lactulose and rifaximin. Ultrasound of abdomen showed no cholelithiasis and no evidence of bleeding, and urinalysis was positive for bilirubin. On 27 Feb 2015 (Day 366), the subject was discharged from the hospital. On 16 Apr 2015 (Day 414), the subject was withdrawn from study due to increased blood bilirubin and received the last dose of the study drug on 25 Feb 2015 (Day 364). The subject recovered from fall, malaise, wound hematoma, and hepatic encephalopathy. The subject did not recover from increased blood bilirubin, jaundice, fatigue, dizziness, and somnolence. The Investigator considered increased blood bilirubin serious and possibly related to the study drug; hepatic encephalopathy, malaise, jaundice, fatigue, dizziness, and somnolence nonserious and possibly related to the study drug; fall on head and wound hematoma on head nonserious and not related to the study drug.

On 16 Jul 2016 (Day 871, 507 days after the last dose), the subject died due to disease progression.

Table Total Bilirubin

Laboratory Test Date (Day)	**Total Bilirubin Central Laboratory NR: 0 – 18.8 umol/L Local Laboratory NR: 0 – 17.1 umol/L**
(Screening) 18 Feb 2014 (Day –9)	18.3 CNR
(Baseline) 26 Feb 2014 (Day –1)	19 CNR
09 Oct 2014 (Day 225)	45 CNR
26 Feb 2015 (Day 365)	121.6 CNR
03 Mar 2015 (Day 370)	124.83 LNR
06 Mar 2015 (Day 373)	117.99 LNR
09 Mar 2015 (Day 376)	128.25 LNR
19 Mar 2015 (Day 386)	97.47 LNR
02 Apr 2015 (Day 400)	85.5 LNR
09 Apr 2015 (Day 407)	78.66 LNR
16 Apr 2015 (Day 414)	65.2 CNR

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

Subject Number	18081001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01543-CLI-DE
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatorenal syndrome, Hepatic encephalopathy
AE(s) Leading to Discontinuation	Impaired healing

A 54-year-old white male was diagnosed with hepatocellular carcinoma in Nov 2013. Significant medical history included chronic obstructive pulmonary disease, type 2 diabetes mellitus, esophageal varices, hypertension, hyperthyroidism, hepatic cirrhosis, left nephrolithiasis, and psoriasis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included bekform, ciprofloxacin, domperidone, furosemide, levothyroxine, metamizole, metformin, metoclopramide, nystatin, pantoprazole, penicillin, propranolol, spironolactone, tiotropium, torasemide, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left liver lobe. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 08 Jul 2014 (Day 198), the subject experienced kidney infection (Grade 3) and was treated with ciprofloxacin. On 10 Jul 2014 (Day 200), the study drug was interrupted due to kidney infection. On the same day (Day 200), the subject experienced impaired healing (wound healing delayed at left tibia; Grade 3) which started as Grade 1 on 02 Jun 2014 (Day 162). On 16 Jul 2014 (Day 206), the subject experienced hepatorenal syndrome (Grade 4) and hepatic encephalopathy (Grade 4). The study drug remained interrupted due to impaired healing, hepatorenal syndrome, and hepatic encephalopathy. On 19 Jul 2014 (Day 209), laboratory tests showed urea 51.84 (units not provided) (NR: not provided) and total bilirubin 23.94 umol/L (NR: 0 – 18.81). On 20 Jul 2014 (Day 210), laboratory tests showed total bilirubin 30.78 umol/L, ALP 273 U/L (NR: 0 –130), AST 258 U/L (NR: 0 – 50), and creatinine 468.52 umol/L (NR: 0 – 123.76). On 24 Jul 2014 (Day 214), laboratory tests showed blood ammonia 201.60536 umol/L (NR: 0 – 57.112). The subject was treated with furosemide. The subject did not recover from kidney infection, impaired healing, hepatorenal syndrome, and hepatic encephalopathy. On 08 Aug 2014 (Day 229), the subject was withdrawn from the study due to impaired healing and received the last dose of study drug on 09 Jul 2014 (Day 199). The Investigator considered hepatorenal syndrome, hepatic encephalopathy serious and possibly related to study drug; kidney infection, impaired healing nonserious and possibly related to the study drug.

On 15 Aug 2014 (Day 236, 37 days after the last dose), the subject died due to unknown reason.

Subject Number	19011028
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006197
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Necrotising bronchiolitis

A 63-year-old white male was diagnosed with hepatocellular carcinoma on 22 Jan 2015. Significant medical history included chronic cholecystitis, hemorrhoids, chronic pancreatitis, gastroesophageal reflux disease, chronic hepatitis C, duodenal ulcer, hepatitis A, paraneoplastic rash, peptic ulcer, esophageal varices, colitis, thrombocytopenia, and hepatic cirrhosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylcysteine, aluminium phosphate, solcoseryl (blood, calf, deprot, LMW portion), carvedilol, ciprofloxacin, dexamethasone, enalapril, etamsilate, fenspiride, furosemide, lactulose, levofloxacin, mebeverine, omeprazole, pancreatin, pimafucort, rifaximin, spironolactone, troxerutin, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 17 Mar 2015 (Day 1), treatment with study drug was initiated.

On 28 Mar 2015 (Day 12), the subject experienced asthenia (Grade 2), and was treated with dexamethasone. On 31 Mar 2015 (Day 15), the study drug dose was reduced to 8 mg/day due to asthenia. The subject was recovering from asthenia. The Investigator considered asthenia nonserious and possibly related to the study drug.

On 02 Apr 2015 (Day 17), the subject experienced necrotizing bronchiolitis (Grade 2) and also experienced hemoptysis (Grade 1). On 12 Apr 2015 (Day 27), the hemoptysis worsened to Grade 2. On 12 Apr 2015 (Day 27), the study drug was interrupted due to necrotizing bronchiolitis and hemoptysis. On 21 Apr 2015 (Day 36), the subject was hospitalized for further management. Treatment included etamsilate, fenspiride, and solcoseryl (blood, calf, deprot, LMW portion). On 22 Apr 2015 (Day 37), the subject recovered from hemoptysis. On 23 Apr 2015 (Day 32), the subject underwent bronchoscopy which confirmed ulcerative necrotizing bronchiolitis. On 27 Apr 2015 (Day 42), necrotizing bronchiolitis improved to Grade 1. On 28 Apr 2015 (Day 43), the study drug was resumed at a reduced dose of 4 mg/day due to necrotizing bronchiolitis. The subject did not recover from necrotizing bronchiolitis. The Investigator considered necrotizing bronchiolitis serious and probably related to the study drug; hemoptysis nonserious and possibly related to the study drug.

On 30 Jun 2015 (Day 106), the subject had hemoptysis (Grade 2) and necrotizing bronchiolitis worsened to Grade 2. The study drug was interrupted due to hemoptysis and necrotizing bronchiolitis. On 06 Jul 2015 (Day 112), the subject recovered from hemoptysis. On 07 Jul 2015 (Day 113), the subject experienced idiopathic pulmonary fibrosis (Grade 2) and necrotizing bronchiolitis improved to Grade 1. The study drug remained interrupted due to idiopathic pulmonary fibrosis. Treatment included etamsilate and dexamethasone. On

20 Jul 2015 (Day 126), the subject recovered from necrotizing bronchiolitis. The subject was recovering from idiopathic pulmonary fibrosis. The Investigator considered necrotizing bronchiolitis and idiopathic pulmonary fibrosis nonserious and probably related to the study drug; hemoptysis nonserious and possibly related to the study drug.

On 07 Jul 2015 (Day 113), tumor response assessment showed disease progression. On 09 Jul 2015 (Day 115), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 29 Jun 2015 (Day 105).

On 11 Sep 2015 (Day 179, 74 days after the dose), the subject died due to disease progression.

Subject Number	19021003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006253
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Jaundice cholestatic, Thrombophlebitis, Deep vein thrombosis, Cellulitis

A 53-year-old white male was diagnosed with hepatocellular carcinoma on 21 Jan 2014. Significant medical history included bile duct stent insertion, chronic cholecystitis, left renal cyst, decreased appetite, type 2 diabetes mellitus, fatigue, hepatitis B, decreased weight, liver biopsy, laparotomy, and upper abdominal pain. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included ademetionine, aprotinin, capiven, ceftriaxone, human insulin (protaphane HM), hymecromone, insulin (actrapid HP penfill), ketamine, mebeverine, metronidazole, nadroparin, omeprazole, ornithine, pancreatin, pentoxifylline, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver, left lobe of liver, and pancreatic mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 10 Apr 2015 (Day 410), the subject experienced jaundice (Grade 1) and upper abdominal pain (right hypochondrium; Grade 3). On 13 Apr 2015 (Day 413), the subject experienced cholestatic jaundice (Grade 4) and the study drug was interrupted due to cholestatic jaundice. The MRI of the abdomen showed blockage of the bile ducts. On 14 Apr 2015 (Day 414), the subject was hospitalized for cholestatic jaundice. On 15 Apr 2015 (Day 415), the subject underwent stenting of the bile duct and was also treated with mebeverine, hymecromone, ursodeoxycholic acid, and ornithine. On 21 Apr 2015 (Day 421), the subject recovered from cholestatic jaundice and was discharged from the hospital. On 21 Apr 2015 (Day 421), the subject experienced increased blood bilirubin (Grade 3) with total bilirubin 94.9 umol/L (NR: 0 – 18.8), increased gamma-glutamyltransferase (Grade 3) with GGT 660 U/L (NR: 10 – 49), increased alkaline phosphatase (Grade 3) with ALP 787 U/L (NR: 43 – 115), increased aspartate aminotransferase (Grade 1) with AST 100 U/L (NR: 10 – 43), and increased alanine aminotransferase (Grade 1) with ALT 131 U/L (NR: 10 – 40). On 28 Apr 2015 (Day 428), increased blood bilirubin and increased alkaline phosphatase improved to Grade 2 and increased alanine aminotransferase worsened to Grade 2. On 29 Apr 2015 (Day 429), the study drug was resumed at a reduced dose of 8 mg/day due to cholestatic jaundice. On 10 May 2015 (Day 440), the subject recovered from jaundice. On 19 May 2015 (Day 449), the subject recovered from increased blood bilirubin with total bilirubin 13.7 umol/L and increased aspartate aminotransferase with AST 37 U/L. On 14 Jul 2015 (Day 505), the subject recovered from increased alanine aminotransferase; on 20 Aug 2015 (Day 542), the subject recovered from increased alkaline phosphatase. The subject was recovering from upper abdominal pain and increased gamma-glutamyltransferase. The Investigator considered cholestatic jaundice serious and not related to the study drug; upper abdominal pain, increased blood bilirubin, increased aspartate aminotransferase, increased alanine aminotransferase, increased alkaline phosphatase, increased gamma-glutamyltransferase, and jaundice nonserious and not related to the study drug.

On 29 May 2015 (Day 459), the subject experienced thrombophlebitis of right leg (Grade 2), pain in right leg (Grade 2), and edema of right leg (Grade 1). On 01 June 2015 (Day 462), the subject was hospitalized for thrombophlebitis. The subject was treated with capiven and pentoxifylline. On 11 Jun 2015 (Day 472), the subject recovered from thrombophlebitis and was discharged from the hospital. The subject was recovering from pain in right leg and edema in right leg. The Investigator considered thrombophlebitis serious and possibly related to the study drug; pain in right leg and edema in right leg nonserious and possibly related to the study drug.

On 26 Jun 2015 (Day 487), the subject was hospitalized for cellulitis of right leg (Grade 3) and deep vein thrombosis (Grade 4). On 26 Jun 2015 (Day 487), the subject also experienced increased white blood cell count (Grade 1) with WBC count 21.2 x10^9/L (NR: 3.7 – 11). The subject underwent surgical debridement of right leg and the study drug was interrupted due to deep vein thrombosis. Treatment included packed red blood cells and plasma transfusion, ceftriaxone, ketamine, metronidazole, and nadroparin. On 01 Jul 2015 (Day 492), the severity of pain in right leg improved to Grade 1. On 14 Jul 2015 (Day 505), the subject recovered from cellulitis of right leg, deep vein thrombosis, and increased white blood cell count. On 21 Jul 2015 (Day 512), the study drug was resumed at the same dose. The subject did not recover from pain in the right leg. The Investigator considered deep vein thrombosis serious and possibly related to the study drug; cellulitis of right leg serious and not related to the study drug; pain in right leg nonserious and possibly related to the study drug; increased white blood cell count nonserious and not related to the study drug.

On 17 Sep 2015 (Day 570), tumor response assessment showed disease progression. On 21 Sep 2015 (Day 574), 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 574).

On 09 Nov 2015 (Day 623, 49 days after the last dose), the subject died due to unknown reason.

Subject Number	19021007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01513-CLI-RU
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Duodenal ulcer, Duodenal ulcer haemorrhage, Umbilical hernia

A 67-year-old white male was diagnosed with hepatocellular carcinoma on 13 Feb 2014. Significant medical history included hepatitis B. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included ademetionine, clemastine, and omeprazole. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and quadrate lobes of liver; paracaval, porta-hepatis, mesenteric, and para-aortic lymphadenopathies. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 27 Mar 2014 (Day 1), treatment with study drug was initiated.

On 16 May 2014 (Day 51), the subject experienced fatigue and melena and was diagnosed with duodenal ulcer (Grade 1). On 19 May 2014 (Day 54), the subject was hospitalized for duodenal ulcer hemorrhage (Grade 3) and duodenal ulcer (Grade 1). The study drug was interrupted due to these events. On 20 May 2014 (Day 55), gastrointestinal tract endoscopy revealed a bleeding duodenal ulcer. The subject was treated with unspecified hemostasis therapy and omeprazole. On 23 May 2014 (Day 58), repeat endoscopy showed chronic duodenal ulcer without bleeding. On 27 May 2014 (Day 62), the subject recovered from duodenal ulcer hemorrhage and was discharged from the hospital. On 29 May 2014 (Day 64), the study drug was resumed at same dose. On 30 Oct 2014 (Day 218), the subject recovered from duodenal ulcer. The Investigator considered duodenal ulcer serious and possibly related to the study drug; duodenal ulcer hemorrhage serious and not related to the study drug.

On 28 Jan 2015 (Day 308), the subject experienced hemoptysis (Grade 3) and the study drug was interrupted due to the event. On 31 Jan 2015 (Day 311), the severity of hemoptysis improved to Grade 1. On 05 Mar 2015 (Day 344), the study drug was resumed at a reduced dose of 8 mg/day due to hemoptysis. On 02 Apr 2015 (Day 372), the subject recovered from hemoptysis. The Investigator considered hemoptysis nonserious and possibly related to study drug.

On 21 Apr 2015 (Day 391), the subject was hospitalized to undergo hernia repair for umbilical hernia. The subject had the umbilical hernia (Grade 1) since 20 Feb 2015 (Day 331). The surgery was uneventful and on 28 Apr 2015 (Day 398), the subject recovered from umbilical hernia and was discharged from the hospital. The Investigator considered umbilical hernia serious and not related to the study drug.

On 07 Nov 2016 (Day 957), tumor response assessment showed disease progression. On 09 Nov 2016 (Day 959), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on the same day (Day 959).

On 27 Dec 2016 (Day 1007, 48 days after the last dose), the subject died due to disease progression.

Subject Number	19031019
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-016371
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Renal cell carcinoma
AE(s) Leading to Discontinuation	Renal cell carcinoma

A 66-year-old white male was diagnosed with hepatocellular carcinoma on 19 Jan 2006. Significant medical history included fatigue and hepatitis B. Previous anticancer therapies included hepatectomy (2x). Prior and concomitant medications included ademetionine. At Screening, tumor assessments of target/non-target lesions via CT scan showed retrosternal, bifurcational, and paratracheal lymphadenopathies. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 15 May 2015 (Day 1), treatment with study drug was initiated.

On 21 Dec 2015 (Day 221), the CT scan of abdomen showed right kidney mass and subject was diagnosed with renal cell carcinoma (Grade 4).

On 17 Mar 2016 (Day 308), the subject was withdrawn from the study due to renal cell carcinoma and the subject received the last dose on 16 Mar 2016 (Day 307).

On 04 Apr 2016 (Day 326), the subject was hospitalized for further treatment of renal cell carcinoma. On 05 Apr 2016 (Day 327), the subject underwent nephrectomy of right kidney. On the same day (Day 327), the subject recovered from renal cell carcinoma. The Investigator considered renal cell carcinoma serious and not related to study drug.

Subject Number	20021005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006670
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy (3x), Diarrhoea, Umbilical hernia
AE(s) Leading to Discontinuation	Umbilical hernia

A 63-year-old white male was diagnosed with hepatocellular carcinoma in Oct 2014. Significant medical history included alcohol abuse, atrial fibrillation, Barrett's esophagus, esophageal variceal ligation, hepatic cirrhosis, esophageal varices, pneumonia, and portal hypertension. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylcysteine, alizapride, amoxicillin w/clavulanate potassium, augmentin, befact, calcium carbonate, cathejell lidocain, cefuroxime, ciprofloxacin, clindamycin, colecalciferol, dextrose and sodium chloride injection, enoxaparin, furosemide, human albumin, insulin, isosorbide dinitrate, lactulose, lekovit ca, lidocaine, loperamide, midazolam, movicol, neomycin, pantoprazole, paracetamol, phenylephrine, phytomenadione, potassium phosphate monobasic, povidone-iodine, propranolol, saccharomyces boulardii, silver protein, terlipressin, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of the liver, and multiple subcentimetric lesions in left and right lobes of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 16 Apr 2015 (Day 1), treatment with study drug was initiated.

On 02 May 2015 (Day 17), the subject experienced hepatic encephalopathy (Grade 3). On 08 May 2015 (Day 23), the subject was hospitalized for hepatic encephalopathy associated with symptoms of sleepiness, weakness, slight icterus in eyes, flapping tremor, fatigue, tachycardia, and slow response. The subject also experienced hypertension (Grade 3) with BP of 160/100 mmHg. The subject was treated with lactulose, befact, and propranolol. On 09 May 2015 (Day 24), laboratory tests showed AST 82 U/L (NR: 0 – 35), ALP 192 U/L (NR: 56 – 119), total bilirubin 47.88 umol/L (NR: 5.13 – 20.52), LDH 365 U/L (NR: 84 – 246), and albumin 28.6 g/L (NR: 32 – 48). On 12 May 2015 (Day 27), the study drug dose was reduced to 8 mg/day due to hepatic encephalopathy and hypertension. On 15 May 2015 (Day 30), the subject recovered from hypertension and was discharged from the hospital on 19 May 2015 (Day 34). On 27 May 2015 (Day 42), the subject recovered from hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and possibly related to study drug; hypertension nonserious and possibly related to the study drug.

On 30 Dec 2015 (Day 259), the subject experienced diarrhea (Grade 3), which was started as Grade 2 on 19 Jun 2015 (Day 65). On 02 Jan 2016 (Day 262), the subject was hospitalized for diarrhea and treated with loperamide, saccharomyces boulardii, dextrose and sodium chloride injection, potassium phosphate monobasic, phytomenadione, movicol, and calcium carbonate. On 03 Jan 2016 (Day 263), the study drug was interrupted due to diarrhea. On 07 Jan 2016 (Day 267), the subject underwent colonoscopy and the results were normal. On 10 Jan 2016 (Day 270), the subject experienced ascites (Grade 3). The subject was treated with human

albumin, furosemide, and lidocaine. The subject underwent paracentesis. On 12 Jan 2016 (Day 272), the study drug was resumed at reduced dose of 4 mg/day due to diarrhea. On 22 Jan 2016 (Day 282), the severity of diarrhea improved to Grade 2. The subject did not recover from diarrhea and ascites. The Investigator considered diarrhea serious and possibly related to study drug; ascites nonserious and possibly related to study drug and disease progression.

On 22 Jan 2016 (Day 282), tumor response assessment showed disease progression. The Investigator allowed the subject to continue taking the study drug.

On 04 Feb 2016 (Day 295), the subject was hospitalized for hepatic encephalopathy (Grade 3) with symptoms of confusion and weakness. Laboratory tests showed AST 69 U/L, ALP 371 U/L, ALT 66 U/L (NR: 0 – 45), albumin 21 g/L, ammonia 124 umol/L (NR: 0 – 32), and total bilirubin 44.46 umol/L. The subject was treated with lactulose and neomycin. On 06 Feb 2016 (Day 297), the study drug was interrupted due to hepatic encephalopathy. On 08 Feb 2016 (Day 299), the study drug was resumed at same dose. On 09 Feb 2016 (Day 300), the subject recovered from hepatic encephalopathy and discharged from the hospital. The Investigator considered hepatic encephalopathy serious and not related to the study drug but related to disease progression.

On 13 Feb 2016 (Day 304), the subject was hospitalized for hepatic encephalopathy (Grade 3). Laboratory tests showed AST 125 U/L, ALT 81 U/L, ALP 396 U/L, total bilirubin 37.62 umol/L, GGT 254 U/L (NR: 15 – 55), and ammonia 59 umol/L. The subject was treated with lactulose, amoxicillin w/clavulanate potassium, and augmentin. On the same day (Day 304), the study drug was interrupted due to hepatic encephalopathy. On 17 Feb 2016 (Day 308), laboratory tests showed albumin 23 g/L (NR: 35 – 55), ALP 288 U/L (NR: 43 – 115), AST 108 U/L (NR: 10 – 43), GGT 174 U/L (NR: 10 – 49), and total bilirubin 25.5 umol/L (NR: 0 – 18.8). On the same day (Day 308), the study drug resumed at a reduced frequency of 4 mg every other day due to hepatic encephalopathy. On 18 Feb 2016 (Day 309), the subject recovered from hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and not related to the study drug but related to disease progression.

On 23 Feb 2016 (Day 314), the subject was hospitalized for umbilical hernia (related to ascites; Grade 3) with symptoms of abdominal swelling and severe pain. Laboratory tests showed AST 99 U/L (NR: 0 – 35), ALT 70 U/L (NR: 0 – 45), ALP 403 U/L (NR: 56 – 119), and total bilirubin 42.75 umol/L (NR: 5.13 – 20.52). The subject was treated with paracetamol, alizapride, and tramadol. On 24 Feb 2016 (Day 315), the study drug was withdrawn due to umbilical hernia. On 25 Feb 2016 (Day 316), the subject underwent umbilical hernia repair and recovered on the same day. On 26 Feb 2016 (Day 317), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 23 Feb 2016 (Day 314). The Investigator considered umbilical hernia serious and not related to the study drug but related to disease progression.

On 16 Jun 2016 (Day 428, 114 days after the last dose), the subject died due to disease progression.

Subject Number	21031005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01550-CLI-ES
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy (2x)
AE(s) Leading to Discontinuation	Hepatic encephalopathy

A 76-year-old white female was diagnosed with hepatocellular carcinoma on 10 Jul 2013. Significant medical history included arterial hypertension, breast cancer, hereditary hemochromatosis, type 2 diabetes mellitus, abscess drainage, and esophageal varices. Previous anticancer therapies included hepatectomy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, ceftriaxone, cefuroxime, glimepiride, human insulin, insulin glargine, lactulose, metformin, metformin w/sitagliptin, metoclopramide, propranolol, and spironolactone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and lung metastasis. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 23 Jul 2014 (Day 7), the subject was hospitalized for hepatic encephalopathy (Grade 3) and also experienced diabetic metabolic decompensation (Grade 3), asthenia (Grade 2), and urinary tract infection (Grade 2). The study drug was interrupted due to hepatic encephalopathy and urinary tract infection. On 26 Jul 2014 (Day 10), the subject experienced hypertension (Grade 3) with BP 191/80 mmHg. On 27 Jul 2014 (Day 11), the subject experienced hyperbilirubinemia (Grade 3) with total bilirubin 68.4 umol/L (NR: 1.71 – 18.81). The subject was treated with metoclopramide, lactulose, cefuroxime, human insulin, insulin glargine, glimepiride, and amlodipine. On 26 Jul 2014 (Day 10), the subject recovered from hypertension and on 28 Jul 2014 (Day 12), the subject recovered from hepatic encephalopathy, diabetic metabolic decompensation, and urinary tract infection. On 30 Jul 2014 (Day 14), the study drug remained interrupted due to asthenia. On 30 Jul 2014 (Day 14), the subject recovered from hyperbilirubinemia. Laboratory tests showed albumin 34 g/L (NR: 35 – 55), ALP 201 U/L (NR: 30 – 115), ALT 56 U/L (NR: 10 – 33), AST 63 U/L (NR: 10 – 36), and CRP 9 mg/L (NR: 0 – 5). On 13 Aug 2014 (Day 28), the subject recovered from asthenia. On 13 Aug 2014 (Day 28), the study drug was resumed at a reduced dose of 8 mg/day due to hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and probably related to study drug; diabetic metabolic decompensation nonserious and possibly related to the study drug; asthenia, hypertension, and hyperbilirubinemia nonserious and probably related to study drug; urinary tract infection nonserious and not related to study drug.

On 01 Sep 2014 (Day 47), the subject experienced hepatic encephalopathy (Grade 2). On 02 Sep 2014 (Day 48), the study drug was interrupted due to hepatic encephalopathy. On 10 Sep 2014 (Day 56), the subject experienced asthenia (Grade 2). Laboratory tests showed total bilirubin 25.5 umol/L (NR: 1.7 – 18.8), ALP 285 U/L, ALT 82 U/L, and AST 83 U/L.

On 11 Sep 2014 (Day 57), the study drug remained interrupted due to asthenia. On 23 Sep 2014 (Day 69), the subject recovered from hepatic encephalopathy and asthenia. On 24 Sep 2014 (Day 70), the study drug was resumed at a reduced dose of 4 mg/day due to hepatic encephalopathy. The Investigator considered hepatic encephalopathy and asthenia nonserious and probably related to study drug.

On 23 Oct 2014 (Day 99), the subject experienced asthenia (Grade 2). On 31 Oct 2014 (Day 107), the subject was hospitalized for hepatic encephalopathy (Grade 3) and the study drug was interrupted due to this event and the subject was treated with ceftriaxone and lactulose. Laboratory tests showed AST 50 U/L (NR: 2 – 37), ALT 49 U/L (NR: 2 – 40), ALP 156 U/L (NR: 40 – 129), and total bilirubin 76.95 umol/L (NR: 1.71 – 18.81). On 07 Nov 2014 (Day 114), the subject recovered from hepatic encephalopathy and was discharged from the hospital. On 21 Nov 2014 (Day 128), the subject was withdrawn from the study due to hepatic encephalopathy. The subject received the last dose of the study drug on 30 Oct 2014 (Day 106). The subject did not recover from asthenia. The Investigator considered hepatic encephalopathy serious and probably related to study drug; asthenia nonserious and probably related to the study drug.

On 01 Apr 2015 (Day 259, 153 days after the last dose), the subject died due to clinical disease progression.

Subject Number	21031012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010869
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Urinary tract infection (2x), Transient ischaemic attack

A 59-year-old white male was diagnosed with hepatocellular carcinoma on 30 Oct 2014. Significant medical history included benign prostatic hyperplasia, depression, type 2 diabetes mellitus, polyneuropathy, hypercholesterolemia, myelopathy (intermittent urinary tube placement due to myelopathy), urinary tract infection (multiple episodes), hepatitis C, osteoarthritis (right hand), and limb traumatic amputation (right leg and left distal). Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included acetylsalicylic acid, augmentin, baclofen, ciprofloxacin, citalopram, domperidone, enemas, enoxaparin, insulin glargine, lactulose, metformin, omeprazole, paracetamol, piperacillin/tazobactam, pregabalin, rosuvastatin, silodosin, sitagliptin, venlafaxine, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 29 Jul 2015 (Day 1), treatment with study drug was initiated.

On 28 Sep 2015 (Day 62), the subject was hospitalized for urinary tract infection (Grade 2). Urinalysis showed positive for leukocytes and bacteria; urine culture was positive for Klebsiella. The subject was treated with piperacillin/tazobactam, paracetamol, and ciprofloxacin. On 30 Sep 2015 (Day 64), the study drug was interrupted due to this event. On 03 Oct 2015 (Day 67), the subject recovered from this event and was discharged from the hospital. On 04 Oct 2015 (Day 68), the study drug was resumed at same dose. The Investigator considered urinary tract infection serious and not related to the study drug.

On 04 Nov 2015 (Day 99), the subject experienced diarrhea (Grade 1). On 20 Nov 2015 (Day 115), the subject experienced asthenia (Grade 2) and severity of diarrhea worsened to Grade 2. On the same day (Day 115), the study drug was reduced to 8 mg/day due to these events. On 04 Dec 2015 (Day 129), the subject recovered from diarrhea and was recovering from asthenia. The Investigator considered diarrhea nonserious and possibly related to the study drug; asthenia nonserious and probably related to the study drug.

On 22 Nov 2015 (Day 117), the subject was hospitalized for urinary tract infection (Grade 2) and urinalysis was positive for leucocytes and bacteria; urine culture was positive for Klebsiella. The subject was treated with ciprofloxacin and paracetamol. On 23 Nov 2015 (Day 118), the study drug was interrupted due to this event. On 24 Nov 2015 (Day 119), the subject recovered from urinary tract infection and was discharged from the hospital. On 25 Nov 2015 (Day 120), the study drug was resumed at same dose. The Investigator considered urinary tract infection serious and not related to the study drug.

On 27 Nov 2015 (Day 122), the subject experienced inability to speak with loss of strength and sensation of right upper extremities lasting for 10 minutes, and was hospitalized with a diagnosis of transient ischemic attack (Grade 2). Head CT scan showed no signs of ischemia or hemorrhage. The subject was treated with acetylsalicylic acid and the study drug was interrupted due to this event. On the same day (Day 122), the subject recovered from transient ischemic attack. On 02 Dec 2015 (Day 127), the subject was discharged from hospital. On 03 Dec 2015 (Day 128), the study drug was resumed at same dose. The Investigator considered transient ischemic attack serious and not related to the study drug.

On 02 Feb 2016 (Day 189), tumor response assessment showed disease progression. On 03 Feb 2016 (Day 190), the subject was withdrawn from study due to disease progression and received the last dose of study drug on the same day (Day 190).

Subject Number	21041004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006149
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diarrhoea, Peritonitis bacterial

A 62-year-old white male was diagnosed with hepatocellular carcinoma in Sep 2013. Significant medical history included asthenia, chronic gastritis, chronic hepatitis C, general discomfort, headache, hemorrhoids, hypertension, and psoriasis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included allopurinol, amlodipine, ceftriaxone, cefuroxime, clindamycin, enalapril, enoxaparin, furosemide, human albumin, hydrochlorothiazide, loperamide, lorazepam, meropenem, metamizole, metoclopramide, metronidazole, morphine, omeprazole, pancreatin, pantoprazole, paracetamol, piperacillin/tazobactam, propranolol, rifaximin, spironolactone, valsartan, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed liver lesions at segment IV, VII, and VIII. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 14 Jan 2015 (Day 1), treatment with study drug was initiated.

On 16 Jan 2015 (Day 3), the subject experienced hypertension (Grade 3) with blood pressure of 184/87 mmHg and was treated with enalapril, valsartan, hydrochlorothiazide, and amlodipine. On 21 Jan 2015 (Day 8), the severity of hypertension improved to Grade 1. The subject was recovering from the event. The Investigator considered hypertension nonserious and probably related to the study drug.

On 12 Apr 2015 (Day 89), the subject experienced for worsening of diarrhea (Grade 3) which was ongoing as Grade 1 since 13 Jan 2015 (Day –1). On 20 Apr 2015 (Day 97), the subject was hospitalized for diarrhea and also experienced vomiting (Grade 2) and acute kidney injury (Grade 1). Laboratory test showed creatinine 167.96 umol/L (NR: 61.88 – 106.08). On the same day (Day 97), the study drug was interrupted due to diarrhea and ongoing hypertension. The subject was treated with loperamide, intravenous fluids, and supportive care. On 24 Apr 2015 (Day 101), the subject recovered from vomiting and acute kidney injury. On 25 Apr 2015 (Day 102), the severity of diarrhea improved to Grade 2. On 27 Apr 2015 (Day 104), the subject recovered from diarrhea and hypertension with blood pressure of 110/70 mmHg. On the same day (Day 104), the study drug was resumed at a reduced dose of 8 mg/day due to diarrhea. The Investigator considered diarrhea serious and possibly related to the study drug; hypertension and vomiting nonserious and probably related to the study drug; acute kidney injury nonserious and not related to the study drug.

On 29 Apr 2015 (Day 106), the subject was hospitalized for spontaneous bacterial peritonitis (Grade 3) associated with fever and body temperature of 40 °C. On 30 Apr 2015 (Day 107), the study drug was interrupted due to bacterial peritonitis. The blood cultures were positive for Escherichia coli and the subject was treated with paracetamol, metamizole, pantoprazole,

morphine, propranolol, metoclopramide, metronidazole, piperacillin/tazobactam, rifaximin, lorazepam, meropenem, human albumin, enoxaparin, zolpidem, ceftriaxone, cefuroxime, and omeprazole. On 08 May 2015 (Day 115), the subject recovered from spontaneous bacterial peritonitis and was discharged from the hospital. The Investigator considered spontaneous bacterial peritonitis serious and not related to the study drug.

On 14 May 2015 (Day 121), tumor response assessment showed disease progression. On 25 May 2015 (Day 132), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 29 Apr 2015 (Day 106).

Subject Number	21051001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000124
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Asthenia

A 54-year-old white male was diagnosed with hepatocellular carcinoma on 31 Jan 2014. Significant medical history included drug hypersensitivity to ibuprofen, chronic hepatitis C, esophageal varices, and neck pain (right cervical pain). The subject did not receive any previous anticancer therapies. Prior and concomitant medications included baclofen, chlorpromazine, ciprofloxacin, dexamethasone, dexketoprofen, diazepam, fentanyl, lactulose, loprazolam, lorazepam, lormetazepam, megestrol, metamizole, methylprednisolone, metoclopramide, metronidazole, morphine, movicol, naloxone, nystatin, omeprazole, paracetamol, paroxetine, prednisone, tramadol, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe and gastrohepatic ligament; lymphadenopathies at lower para-esophageal and para-aortic areas. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 05 Mar 2014 (Day 1), treatment with study drug was initiated.

On 18 Mar 2014 (Day 14), the subject experienced increased alanine aminotransferase (Grade 3), increased aspartate aminotransferase (Grade 2), and increased blood bilirubin (Grade 2) with ALT 386 U/L (NR: 10 – 40), AST 168 U/L (NR: 10 – 43), and total bilirubin 35.1 umol/L (NR: 1.7 – 18.8). On 19 Mar 2014 (Day 15), the study drug was interrupted due to increased alanine aminotransferase. On 25 Mar 2014 (Day 21), the subject recovered from increased alanine aminotransferase, increased aspartate aminotransferase, and increased blood bilirubin with ALT 99 U/L, AST 60 U/L, and total bilirubin 14.7 umol/L. On 25 Mar 2014 (Day 21), the study drug was resumed at a reduced dose of 8 mg/day due to increased alanine aminotransferase. The Investigator considered increased alanine aminotransferase, increased aspartate aminotransferase, and increased blood bilirubin nonserious and probably related to the study drug.

On 20 Aug 2014 (Day 169), the subject experienced decreased appetite (Grade 3), which started as Grade 2 on 08 May 2014 (Day 65). On 03 Sep 2014 (Day 183), the study drug was interrupted due to decreased appetite and the subject was treated with megestrol. On 08 Sep 2014 (Day 188), the study drug was resumed at the same dose. The subject did not recover from decreased appetite. The Investigator considered decreased appetite nonserious and possibly related to the study drug.

On 16 Sep 2014 (Day 196), the subject was hospitalized for asthenia (Grade 3), which started as Grade 1 on 27 May 2014 (Day 84). On 17 Sep 2014 (Day 197), the study drug was interrupted due to an ongoing decreased appetite. Treatment included dexamethasone, ciprofloxacin, lormetazepam, prednisone, lorazepam, and methylprednisolone. On 22 Sep 2014 (Day 202), the subject was discharged from the hospital. On 07 Oct 2014 (Day 217), the study drug was

resumed at a reduced dose of 4 mg/day due to decreased appetite. The subject did not recover from asthenia and decreased appetite. The Investigator considered asthenia serious and possibly related to study drug and disease progression; decreased appetite nonserious and possibly related to the study drug.

On 03 Nov 2014 (Day 244), the subject experienced hypophosphatemia (Grade 3) with phosphate 1.1 mg/dL (NR: 2.5 – 4.5). On 04 Nov 2014 (Day 245), the study drug was interrupted due to hypophosphatemia. On 11 Nov 2014 (Day 252), the subject recovered from hypophosphatemia with phosphate 3.1 mg/dL. The Investigator considered hypophosphatemia nonserious and possibly related to the study drug.

On 21 Nov 2014 (Day 262), tumor response assessment showed disease progression. The subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 03 Nov 2014 (Day 244).

On 02 Feb 2015 (Day 335, 91 days after the last dose), the subject died due to disease progression.

Subject Number	24031014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001867
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cholecystitis

A 47-year-old Chinese male was diagnosed with hepatocellular carcinoma on 13 Mar 2014. Significant medical history included ascites, emphysema, cholelithiasis, hepatitis B, left renal cyst, hepatic cirrhosis, skin graft (outside of right thigh), and thermal burn (left hip). Previous anticancer therapies included radiotherapy to liver lesion and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids, anisodamine, ascorbic acid, deoxyribonucleic acid, diisopropylamine, entecavir, esomeprazole, glucose injection, inosine, lappaconitine, levofloxacin, metoprolol, pethidine, potassium, sodium chloride, somatostatin, unspecified herbal and traditional medicine (shenqifuzheng injection, hu gan pian), and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 15 Nov 2014 (Day 10), the subject experienced cholecystitis (Grade 3) and was subsequently admitted to the hospital on 18 Nov 2014 (Day 13). Abdominal x-ray showed no liquid gas level in the abdomen and no free gas under diaphragm and mediastinum. Ultrasound of abdomen confirmed cholecystitis with gallbladder 82 mm x 37 mm in size, gallbladder wall rough and double-layered with 8 mm in thickness, and 3mm hyperechoic spot. The subject was treated with amino acids, levofloxacin, potassium, ascorbic acid, anisodamine, esomeprazole, pethidine, inosine, lappaconitine, and somatostatin. On 19 Nov 2014 (Day 14), the study drug was interrupted due to cholecystitis. On 20 Nov 2014 (Day 15), the subject underwent cholecystectomy with insertion of tube in the gallbladder for drainage. On 25 Nov 2014 (Day 20), the subject was discharged from the hospital. On 15 Dec 2014 (Day 40), the subject recovered from cholecystitis. On 16 Dec 2014 (Day 41), the study drug was resumed at same dose. The Investigator considered cholecystitis serious and possibly related to the study drug.

On 17 Jun 2015 (Day 224), tumor response assessment showed disease progression. On the same Day (Day 224), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug.

On 26 Feb 2016 (Day 478, 254 days after the last dose), the subject died due to disease progression.

Subject Number	24081007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-009971
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Oesophageal varices haemorrhage

A 68-year-old Chinese male was diagnosed with hepatocellular carcinoma on 10 Dec 2014. Significant medical history included chronic gastritis, hepatic cirrhosis, diabetes mellitus, esophageal varices, and hepatitis B. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amino acids, carbazochrome, carbohydrates w/electrolytes, furosemide, glucose injection, glutathione, hemocoagulase, heparin, jia wei bi (methionine and vitamin B1 injection), lactobacillus acidophilus, lansoprazole, medilac-s, nurofen plus, octreotide, omeprazole, pantoprazole, potassium, potassium phosphate monobasic, rabeprazole, rebamipide, retinol with tocopherol/vitamin d/vitamin k, spironolactone, trimebutine, and unspecified herbal and traditional medicine (gu chang zhi xie wan, wei tong ling jiao nang, and si mo tang kou fu ye). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, masses at right lower lung and bilateral lung lobes, and hilus and abdominal aorta lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 17 Dec 2014 (Day 6), the subject experienced abdominal pain (Grade 1), decreased appetite (Grade 1), and fatigue (Grade 1). On 25 Dec 2014 (Day 14), severity of abdominal pain, decreased appetite, and fatigue worsened to Grade 2. On the same day (Day 14), the study drug was interrupted due to decreased appetite and fatigue. The subject was treated with nurofen plus. On 29 Dec 2014 (Day 18), the subject recovered from decreased appetite and fatigue. On 30 Dec 2014 (Day 19), the study drug was resumed at a reduced dose of 8 mg/day due to decreased appetite and fatigue. On 23 Jan 2015 (Day 43), the subject recovered from abdominal pain. The Investigator considered decreased appetite and fatigue nonserious and probably related to the study drug; abdominal pain nonserious and not related to the study drug.

On 01 Jul 2015 (Day 202), the subject experienced esophageal varices hemorrhage (Grade 3). On 03 Jul 2015 (Day 204), the subject vomited dark red blood and was subsequently hospitalized. Endoscopy confirmed esophageal varices. The subject was treated with blood transfusions. On the same day (Day 204), the study drug was interrupted due to this event. On 15 Jul 2015 (Day 216), the study drug was resumed at same dose and the subject was discharged from hospital. On 23 Jul 2015 (Day 224), the subject was re-hospitalized for endoscopic variceal ligation. Laboratory tests showed RBC 3.25 x10^12/L (NR: 4 – 5.6), Hgb 107 g/L (NR: 125 – 170), ALP 153 U/L (NR: 43 – 115), and AST 50 U/L (NR: 10 – 43). The subject was treated with octreotide, glutathione, jia wei bi (methionine and vitamin B1), and pantoprazole. On 27 Jul 2015 (Day 228), the subject underwent esophageal variceal ligation and was treated with omeprazole, carbazochrome, potassium phosphate monobasic, and lansoprazole. On 27 Jul 2015 (Day 228), the subject experienced portal hypertensive

gastropathy (Grade 2). On 03 Aug 2015 (Day 235), the subject was discharged from the hospital. On 04 Aug 2015 (Day 236), the subject recovered from esophageal varices hemorrhage. The subject did not recover from portal hypertensive gastropathy. The Investigator considered esophageal varices hemorrhage serious and not related to the study drug; portal hypertensive gastropathy nonserious and not related to the study drug.

On 08 Jan 2016 (Day 393), the subject experienced ascites (Grade 2) which started as Grade 1 on 23 Jul 2015 (Day 224). On 27 Feb 2016 (Day 443), the study drug was interrupted due to this event. The subject did not recover from ascites. The Investigator considered ascites nonserious and not related to the study drug.

On 19 Apr 2016 (Day 495, 53 days after the last dose), the subject died due to gastrointestinal hemorrhage (alimentary tract hemorrhage related to liver cirrhosis). The subject received the last dose of the study drug on 26 Feb 2016 (Day 442). The Investigator considered gastrointestinal hemorrhage serious and not related to the study drug.

Subject Number	24111005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-008173
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Facial paralysis, Meningioma

A 47-year-old Chinese male was diagnosed with hepatocellular carcinoma on 23 Aug 2011. The subject had no significant medical history. Previous anticancer therapies included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, amoxicillin, atorvastatin, diazepam, ibuprofen, mecobalamin, and metoprolol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 23 Jun 2015 (Day 333), the subject experienced facial paralysis (Grade 3) with pain. The subject was treated with demerol, mecobalamin, and ibuprofen. On 25 Jun 2015 (Day 335), CT scan of head showed no abnormality on the double flank nerve and trigeminal nerve walk line area; slight inflammation on the bilateral maxillary and ethmoid sinuses. Electromyogram showed right facial nerve damage. The study drug dose did not change. The subject was recovering from facial paralysis. The Investigator considered facial paralysis serious (important medical event) and possibly related to the study drug.

On 28 Aug 2015 (Day 399), the subject experienced facial pain (Grade 2), and the subject was treated with diazepam. On 28 Sep 2015 (Day 430), the subject recovered from facial pain. The study drug dose did not change. The Investigator considered facial pain nonserious and not related to the study drug.

On 13 Sep 2015 (Day 415), the subject experienced epistaxis (Grade 1), mouth hemorrhage (Grade 1), and ear hemorrhage (Grade 1). On the same day (Day 415), the subject recovered from these events without any treatment. On 16 Sep 2015 (Day 418), the subject was hospitalized and diagnosed with right meningioma (Grade 4), which was confirmed by head CT scan. On 17 Sep 2015 (Day 419), the subject underwent brain tumor operation (meningioma resection with gamma knife). On 18 Sep 2015 (Day 420), the study drug was interrupted for Investigator's further assessment. On 22 Sep 2015 (Day 424), the study drug was resumed at same dose. On 28 Sep 2015 (Day 430), the subject recovered from meningioma and was discharged from the hospital. The Investigator considered meningioma serious and not related to the study drug; epistaxis, mouth hemorrhage, and ear hemorrhage nonserious and not related to the study drug.

On 20 Oct 2015 (Day 452), tumor response assessment showed disease progression. On 21 Oct 2015 (Day 453), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on the same day.

On 24 Feb 2016 (Day 579, 126 days after the last dose), the subject died due to disease progression.

Subject Number	24111008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-002868
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Coma hepatic

A 49-year-old Chinese male was diagnosed with hepatocellular carcinoma on 20 Jul 2014. Significant medical history included gastroesophageal reflux disease, chronic gastritis, and hepatitis B. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included entecavir, falkamin, hydrotalcite, norfloxacin, and omeprazole. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 19 Dec 2014 (Day 141), the subject felt feeble and experienced involuntary movements. On physical examination, the subject appeared dull. Laboratory tests showed RBC 3.82 x10^12/L (NR: 4 – 5.6), Hgb 139 g/L (NR: 125 – 170), ALP 82 U/L (NR: 43 – 115), GGT 112 U/L (NR: 10 – 49), total bilirubin 18.6 umol/L (NR: 1.7 – 18.8), and BUN 6.07 mmol/L (NR: 1.78 – 7.14). On 27 Dec 2014 (Day 149), the subject was seen by neurologist and was clinically diagnosed with hepatic coma (Grade 4). The subject was treated with falkamin. On 27 Dec 2014 (Day 149), the subject recovered from hepatic coma. On the same day (Day 149), the study drug was interrupted due to this event. The Investigator considered hepatic coma serious (important medical event) and possibly related to the study drug.

On 07 Jan 2015 (Day 160), the subject withdrew from the study by choice and received the last dose of the study drug on 26 Dec 2014 (Day 148).

On 27 Apr 2015 (Day 270, 122 days after the last dose), the subject died due to disease progression.