Subject Number	30011007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01447-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Oesophageal varices haemorrhage (2x)

A 50-year-old Asian male was diagnosed with hepatocellular carcinoma on 24 Apr 2012. Significant medical history included hepatitis B and hepatic cirrhosis. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included cimetropium, entecavir, glucose, hyoscine, lidocaine, pantoprazole, and simeticone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left liver lobe, right lower paratracheal lymphadenopathy, and masses at left upper and right middle lobes of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 16 Oct 2013 (Day 1), treatment with study drug was initiated.

On 31 Jan 2014 (Day 108), the subject was hospitalized for esophageal varices hemorrhage (Grade 2) and the study drug was interrupted due to this event. No intervention was indicated. On 07 Feb 2014 (Day 115), the subject recovered from the event. On 12 Feb 2014 (Day 120), the subject was discharged from the hospital and the study drug was resumed at same dose on 13 Feb 2014 (Day 121). The Investigator considered esophageal varices hemorrhage serious and not related to the study drug.

On 14 Feb 2014 (Day 122), the subject underwent follow up esophagogastroduodenoscopy and on 19 Feb 2014 (Day 127), the subject was hospitalized for esophageal varices hemorrhage (Grade 3). Treatment included glucose, hyoscine, lidocaine, pantoprazole, simeticone, and the study drug was interrupted due to this event. On 25 Feb 2014 (Day 133), repeat esophagogastroduodenoscopy showed several tortuous venous distensions in middle to distal esophagus. On 26 Feb 2014 (Day 134), the subject underwent esophageal variceal ligation. On 27 Feb 2014 (Day 135), the subject recovered from esophageal varices hemorrhage and the subject was discharged from the hospital. On 06 Mar 2014 (Day 142), the study drug was resumed at a reduced dose of 8 mg/day due to esophageal varices hemorrhage. On 31 Mar 2014 (Day 167), the subject underwent repeat esophageal variceal ligation. The Investigator considered esophageal varices hemorrhage serious and not related to the study drug.

On 01 Apr 2014 (Day 168), tumor response assessment showed disease progression. On 08 Apr 2014 (Day 175), 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 175).

On 31 Jan 2015 (Day 473, 298 days after the last dose), the subject died due to disease progression.

Subject Number	30011009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01486-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy

A 50-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Jul 2012. Significant medical history included cholecystectomy, contrast media allergy, gastritis, hepatitis B, and hepatic cirrhosis. Previous anticancer therapies included transcatheter arterial chemoembolization. Prior and concomitant medications included adefovir, chlorphenamine, famotidine, furosemide, glucose, hyoscine, lactulose, lamivudine, lidocaine, pantoprazole, simeticone, and spironolactone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 30 Jan 2014 (Day 22), the subject experienced confusional state (Grade 3). On 05 Feb 2014 (Day 28), study drug was interrupted due to confusional state. On 07 Feb 2014 (Day 30), the subject recovered from this event. On 08 Feb 2014 (Day 31), the study drug was resumed at reduced dose of 8 mg/day due to confusional state. The Investigator considered confusional state nonserious and probably related to study drug.

On 25 Apr 2014 (Day 107), the subject was hospitalized for hepatic encephalopathy (Grade 3) and on the same day, study drug was interrupted due to this event. The subject was treated with lactulose, lactulose enema, glucose, and famotidine. On 27 Apr 2014 (Day 109), the subject recovered from hepatic encephalopathy. The study drug was scheduled to resume on 30 Apr 2014 (Day 112), at a reduced dose of 4 mg/day due to hepatic encephalopathy but the subject missed the dose and the study drug was not resumed. The Investigator considered hepatic encephalopathy serious and possibly related to study drug.

On 29 Apr 2014 (Day 111), the subject experienced ascites (Grade 2). On 29 Apr 2014 (Day 111), tumor response assessment showed disease progression. On 02 May 2014 (Day 114), the subject was withdrawn from study due to disease progression and received the last dose of study drug on 24 Apr 2014 (Day 106). On 05 May 2014 (Day 117), the severity of ascites increased to Grade 3 and the subject underwent paracentesis. The subject was treated with spironolactone and furosemide. The subject did not recover from this event. The Investigator considered ascites nonserious and not related to study drug.

On 23 Dec 2014 (Day 349, 243 days after the last dose), the subject died due to disease progression.

Subject Number	30011017
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003378
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	IgA nephropathy

A 50-year-old Asian female was diagnosed with hepatocellular carcinoma on 06 Jan 2014. Significant medical history included hepatitis B, hepatic cirrhosis, and menopause. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, metformin, mupirocin, olmesartan, and telbivudine. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 29 Oct 2014 (Day 224), the subject experienced proteinuria (Grade 2) with urine protein dipstick 4+, 24h urine protein 1.9545 g/24hr, and creatinine 53 umol/L (NR: 62 – 124). The study drug dose did not change. The subject did not recover from proteinuria. The Investigator considered proteinuria nonserious and possibly related to the study drug.

On 23 Dec 2014 (Day 279), the subject experienced increased gamma-glutamyltransferase (Grade 3) with GGT 171 U/L (NR: 5 – 32). On 27 Dec 2014 (Day 283), the study drug was interrupted due to increased gamma-glutamyltransferase. The subject did not recover from increased gamma-glutamyltransferase. The Investigator considered increased gamma-glutamyltransferase nonserious and possibly related to the study drug.

On 22 Jan 2015 (Day 309), the subject was hospitalized for IgA nephropathy (Grade 1). On 23 Jan 2015 (Day 310), the subject underwent a kidney biopsy for ongoing proteinuria, which confirmed IgA nephropathy. The study drug dose did not change and no other treatment was provided. On 24 Jan 2015 (Day 311), the subject was recovering from IgA nephropathy and was discharged from the hospital. The Investigator considered the IgA nephropathy serious and not related to study drug.

On 30 Jan 2015 (Day 317), tumor response assessment showed disease progression. On 03 Feb 2015 (Day 321), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 26 Dec 2014 (Day 282).

On 24 Dec 2015 (Day 645, 363 days after the last dose), the subject died due to disease progression.

Subject Number	30051001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01395-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy
AE(s) Leading to Discontinuation	Hepatic encephalopathy

A 76-year-old Asian male was diagnosed with hepatocellular carcinoma on 21 Sep 2013. Significant medical history included abdominal pain, chronic gastritis, constipation, esophageal varices, gastroesophageal reflux disease, hepatitis B, and hepatic cirrhosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, calcium polystyrene sulfonate, cefpodoxime, ceftizoxime, diosmectite, furosemide, human albumin, lactulose, livalavin, magnesium, metoclopramide, metronidazole, ornithine, oxycodone, pamidronic acid, pneumococcal vaccine, potassium, propacetamol, rifaximin, silybum marianum, targin, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left and right lobes of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 04 Nov 2013 (Day 8), the subject experienced hepatic encephalopathy (Grade 3) associated with dizziness (Grade 1) and nausea (Grade 1). On 07 Nov 2013 (Day 11), the subject was hospitalized for hepatic encephalopathy. Laboratory tests showed ALT 66 U/L (NR: 5 – 46), AST 136 U/L (NR: 13 – 34), ALP 341 U/L (NR: 47 – 143), ammonia 109.2267 umol/L (NR: 8.5668 – 47.1174), and total bilirubin 59.85 umol/L (NR: 8.55 – 30.78). Treatment included lactulose, metoclopramide, and rifaximin. On 07 Nov 2013 (Day 11), the subject experienced hypertension (Grade 3) with blood pressure 170/103 mmHg and was treated with amlodipine. On the same day (Day 11), the study drug was withdrawn due to hepatic encephalopathy and the subject received the last dose of study drug on the same day (Day 11). On 08 Nov 2013 (Day 12), the severity of hypertension improved to Grade 2. On 10 Nov 2013 (Day 14), the subject experienced diarrhea (Grade 2) and the severity of hypertension improved to Grade 1. On 11 Nov 2013 (Day 15), the subject had pyrexia (Grade 2) with temperature 39.6 ºC. The subject was treated with metronidazole, ceftizoxime, and propacetamol. The blood culture was negative. On 11 Nov 2013 (Day 15), the subject recovered from hepatic encephalopathy and diarrhea. Repeat laboratory tests showed ALT 64 U/L, AST 147 U/L, total bilirubin 80.37 umol/L, and ammonia 30.6977 umol/L. On 12 Nov 2013 (Day 16), the subject recovered from pyrexia. The subject did not recover from hypertension. On 21 Nov 2013 (Day 25), the subject was discharged from the hospital and also recovered from dizziness and nausea that day. The Investigator considered hepatic encephalopathy serious and not related to study drug; pyrexia, diarrhea nonserious and not related to study drug; nausea, hypertension, and dizziness nonserious and possibly related to study drug.

On 04 Aug 2014 (Day 281, 270 days after the last dose), the subject died of unknown cause.

Subject Number	30051002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01408-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Proteinuria, Generalised oedema, Ascites, Abdominal pain

A 57-year-old Asian male was diagnosed with hepatocellular carcinoma on 26 Sep 2013. Significant medical history included ascites, cancer pain, hepatitis B, hypothyroidism, hepatic cirrhosis, portal vein thrombosis, and metastases to lung. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylcysteine, almagate, amino acids, amlodipine, benzydamine, beszyme, calcium polystyrene sulfonate, celecoxib, chlorphenamine, cimetidine, clinimix, corydalis vanhusuo tuber w/ipomoea nil seed, cyanocobalamin, ecabet, entecavir, falkamin, famotidine, fentanyl, fexofenadine, furosemide, godex, human albumin, hyoscine, ketoprofen, lansoprazole, levothyroxine, linalavin, metoclopramide, morphine, mosapride, multitrace, oxycodone, pethidine, propofol, rabeprazole, simeticone, sodium bicarbonate, sucralfate, spironolactone, targin, teprenone, tramadol, ursodeoxycholic acid, valsartan, and vitamins (MVI inj). At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes; aortocaval and para-aortic lymphadenopathies. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 05 Nov 2013 (Day 1), treatment with study drug was initiated.

On 28 Nov 2013 (Day 24), the subject experienced proteinuria (Grade 2) and generalized edema (Grade 2). Laboratory tests showed urine protein dipstick 2+, 24h urine protein 3.087 g/24hr, and albumin 30 g/L (NR: 35 – 55). On 03 Dec 2013 (Day 29), the study drug was interrupted due to these events. On 04 Dec 2013 (Day 30), the subject was hospitalized for both proteinuria and generalized edema. Treatment included spironolactone, furosemide, and valsartan. On 06 Dec 2013 (Day 32), the subject recovered from proteinuria and generalized edema, and the urine protein dipstick was negative. The subject was discharged from the hospital. The Investigator considered proteinuria and generalized edema serious and probably related to study drug.

On 23 Dec 2013 (Day 49), the subject experienced ascites (Grade 3). On 24 Dec 2013 (Day 50), the subject was hospitalized for abdominal pain (Grade 3) and ascites, and underwent paracentesis. The study drug remained interrupted due to abdominal pain. Treatment included targin, oxycodone, fentanyl, morphine, tramadol, ketoprofen, hyoscine, and pethidine. On 27 Dec 2013 (Day 53), the laboratory tests showed albumin 32 g/L, total bilirubin 44.3 umol/L (NR: 1.7 – 18.8), ALP 260 U/L (NR: 43 – 115), ALT 16 U/L (NR: 10 – 40), and AST 212 U/L (NR: 10 – 43). On 03 Jan 2014 (Day 60), the subject recovered from ascites. On 08 Jan 2014 (Day 65), the severity of abdominal pain improved to Grade 1. The outcome of abdominal pain was unknown. The Investigator considered abdominal pain and ascites serious and not related to study drug.

On 08 Jan 2014 (Day 65), the subject was withdrawn from the study as the subject was lost to follow up and received the last dose of study drug on 02 Dec 2013 (Day 28).

On 22 Feb 2014 (Day 110, 82 days after the last dose), the subject died due to unknown reason.

Subject Number	30051008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011409
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cancer pain
AE(s) Leading to Discontinuation	Cancer pain

A 46-year-old Asian male was diagnosed with hepatocellular carcinoma on 03 Feb 2014. Significant medical history included hepatitis B and gastritis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included almagate, ambroxol acefyllinate, ascorbic acid w/biotin/calcium/carbohydrates, benproperine, benzydamine, corydalis yanhusuo tuber w/ipomoea nil seed, ecabet, esomeprazole, godex, hydromorphone, hyoscine, loperamide, magnesium oxide, metoclopramide, mosapride, myprodol, optiderm, oxycodone, paracetamol, propofol, ramosetron, silybum marianum, tranexamic acid, ultracet, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and quadrate lobe of liver, and aggravated hematogenous lung metastasis. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 02 Sep 2014 (Day 197), the subject experienced cancer pain (abdominal pain related to cancer; Grade 2). The subject was treated with oxycodone. The study drug dose did not change. The subject did not recover from this event. The Investigator considered cancer pain nonserious and not related to the study drug.

On 18 Oct 2015 (Day 608), the subject was hospitalized for worsening cancer pain (Grade 3). On 21 Oct 2015 (Day 611), the study drug was interrupted due to cancer pain and the subject was treated with myprodol. On 10 Nov 2015 (Day 631), the subject was withdrawn from study by choice secondary to cancer pain. The subject received the last dose of the study drug on 20 Oct 2015 (Day 610). The outcome of cancer pain was unknown. The Investigator considered cancer pain serious and not related to the study drug.

On 24 Nov 2015 (Day 645, 35 days after the last dose), the subject died due to unknown reason.

Subject Number	30051012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000100
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Pyrexia, Pneumonia aspiration

A 57-year-old Asian male was diagnosed with hepatocellular carcinoma in Oct 2012. Significant medical history included chronic obstructive pulmonary disease, chronic gastritis, constipation, diabetes mellitus, dysphagia, hepatitis B, hypertension, hepatic cirrhosis, right flank pain, metastases to bone (skull), and dysphonia. Previous anticancer therapies included transcatheter arterial chemoembolization, radiotherapy to 8th rib metastases, and left occipital skull. Prior and concomitant medications included acetylcysteine, amino acids, amphotericin b, bactrim, budesonide, carol-f, chlorphenamine, clarithromycin, codeine, cough s, diapride forte, entecavir, fentanyl, ganciclovir, human albumin, hydrocortisone, hydromorphone, ipratropium, lenograstim, meropenem, mg tna, morphine, oxycodone, paracetamol, piperacillin, potassium, potassium phosphate monobasic, prednisolone, propacetamol, salbutamol, silybum marianum, targin, tramadol, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left liver lobe, lymph node at rib, and mass at skull. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 09 Sep 2014 (Day 8), the subject was hospitalized for pyrexia (Grade 1) with body temperature 38.3 ºC and aspiration pneumonia (Grade 3) from ingesting food. Chest CT showed consolidation in bilateral lobes, subpleural air in the right lung with defect of right pleura, ruled out pleural-abdominal fistula formation, probably perihepatic biloma rupture at the liver dome into the pleura and lung, related necrotizing pneumonia at right lower lobe of lung, and associated bronchiolitis at bilateral lower lobes of lung. The subject was treated with propacetamol, clarithromycin, and piperacillin. On the same day (Day 8), the study drug was interrupted and tumor response assessment showed disease progression. The subject recovered from pyrexia. On 14 Sep 2014 (Day 13), the subject recovered from aspiration pneumonia. The Investigator considered pyrexia and aspiration pneumonia serious and not related to the study drug.

On 06 Oct 2014 (Day 35), the subject was withdrawn from the study due to disease progression. The subject received the last dose of study drug on 08 Sep 2014 (Day 7).

Subject Number	30061003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000311
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Bile duct obstruction (3x), Pneumonia, Acute kidney injury
AE(s) Leading to Discontinuation	Bile duct obstruction

A 58-year-old Asian male was diagnosed with hepatocellular carcinoma on 30 May 2013. Significant medical history included ascites, duodenal ulcer, esophageal varices, hypertension, alcoholic cirrhosis, and spinal column stenosis. Previous anticancer therapies included radiotherapy to caudate lobe of liver and transcatheter arterial chemoembolization. Prior and concomitant medications included acetylcysteine, amino acids, amlodipine, ascorbic acid w/biotin/calcium/carbohydrates, bambuterol, benexate, benzydamine, biosol, calcium acetate, calcium gluconate, calcium polystyrene sulfonate, cefepime, cefmetazole, cefotaxime, cefpodoxime, cefprozil, celecoxib, chlorhexidine, cimetropium, ciprofloxacin, codeine, cough s, de shuang, duloxetine, erdosteine, esomeprazole, fentanyl, festal plus, fexofenadine, flomoxef, flumazenil, fusidic acid, glucose, hepatamine, human albumin, hyaluronidase, hydromorphone, insulin, ipratropium, itopride, ketoconazole, ketoprofen, lactobacillus acidophilus, lactulose, lansoprazole, levobupivacaine, levodropropizine, levofloxacin, levothyroxine, lidocaine, mecobalamin, megestrol, meropenem, metoclopramide, metronidazole, midazolam, morphine, mupirocin, nafamostat, oseltamivir, oxycodone, pantoprazole, paracetamol, pepsane, pethidine, phytomenadione, piperacillin sodium w/tazobactam, potassium, pronase, propacetamol, propranolol, pseudoephedrine, rabeprazole, rifaximin, ringer-lactate, simeticone, smoflipid, sodium bicarbonate, sodium chloride, sucralfate, targin, terlipressin, theobromine, thiamine, torasemide, triamcinolone, ultracet, urea, ursodeoxycholic acid, and vitamins. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right, caudate, and quadrate lobes of the liver; CT scan showed bilateral lung masses. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 16 Jan 2014 (Day 1), treatment with study drug was initiated.

On 23 Sep 2014 (Day 251), the subject was hospitalized for bile duct obstruction (Grade 3). The study drug was interrupted due to this event. Laboratory tests showed ALP 384 U/L (NR: 43 – 115), ALT 212 U/L (NR: 10 – 40), AST 179 U/L (NR: 10 – 43), total bilirubin 62.1 umol/L (NR: 0 – 18.8), direct bilirubin 3.25 mg/dL (NR: 0.09 – 0.30), and GGT 309 U/L (NR: 10 – 49). On 25 Sep 2014 (Day 253), the subject experienced abdominal pain (Grade 2). The subject underwent endoscopic retrograde cholangiopancreatography (ERCP) with biliary drainage insertion and was also treated with cefotaxime, cefpodoxime, ciprofloxacin, oxycodone, midazolam, meropenem, nafamostat, pethidine, propacetamol, pronase, fentanyl, and targin. On 15 Oct 2014 (Day 273), the subject underwent change of biliary drainage. On 21 Oct 2014 (Day 279), the severity of bile duct obstruction improved to Grade 2. On 24 Oct 2014 (Day 282), the study drug dose was resumed at the same dose. On 28 Oct 2014, the subject was discharged from the hospital.

On 31 Oct 2014 (Day 289), the study drug was again interrupted due to bile duct obstruction. On 04 Nov 2014 (Day 293), laboratory test showed total bilirubin 55.1 umol/L and direct bilirubin 2.5 mg/dL. The subject was re-admitted to the hospital for further evaluation. On 06 Nov 2014 (Day 295), the subject underwent ERCP with biliary drainage change. On 10 Nov 2014 (Day 299), the subject recovered from abdominal pain. On 13 Nov 2014 (Day 302), the study drug dose was resumed at same dose. On 14 Nov 2014 (Day 303), the subject recovered from bile duct obstruction with total bilirubin 16.9 umol/L. The Investigator considered bile duct obstruction serious and not related to the study drug but related to the disease progression; abdominal pain nonserious and not related to the study drug.

On 24 Dec 2014 (Day 343), the subject was hospitalized for bile duct obstruction (Grade 2). Laboratory tests showed total bilirubin 28.044 umol/L (NR: 1.71 – 20.52) and the subject underwent biliary drainage change. The study drug was interrupted due to bile duct obstruction. On 29 Dec 2014 (Day 348), the subject experienced pneumonia (Grade 2). Abdomen CT scan showed bile duct obstruction and chest CT scan showed hematogenous metastases, passive atelectasis, and pneumonia. The subject was also treated with acetylcysteine, amino acids, cefepime, cefotaxime, ciprofloxacin, cough s, codeine, metronidazole, midazolam, propacetamol, erdosteine, levodropropizine, ipratropium, piperacillin sodium w/tazobactam, and meropenem. On 06 Jan 2015 (Day 356), the study drug was resumed at the same dose. On 10 Jan 2015 (Day 360), the study drug was interrupted due to pneumonia. On 16 Jan 2015 (Day 366), the subject recovered from bile duct obstruction. On 22 Jan 2015 (Day 372), the study drug dose was resumed at same dose. On 26 Jan 2015 (Day 376), the subject recovered from pneumonia. The Investigator considered bile duct obstruction and pneumonia serious and not related to the study drug. The Investigator considered bile duct obstruction serious and not related to the study drug.

On 02 Feb 2015 (Day 383), the subject was re-hospitalized for bile duct obstruction (Grade 3) and acute kidney injury (Grade 3). The subject also experienced hyperkalemia (Grade 3). The study drug was interrupted on the same day (Day 383) due to these events. Laboratory tests showed albumin 31 g/L (NR: 35 – 55), ALP 205 U/L, AST 73 U/L, total bilirubin 72.8 umol/L, GGT 110 U/L, BUN 28.56 mmol/L (NR: 1.78 – 7.14), creatinine 645 umol/L (NR: 62 – 124), potassium 6.67 mmol/L (NR: 3.5 – 5.3), and sodium 127 mmol/L (NR: 133 – 145). The subject underwent endoscopic retrograde biliary drainage change and was also treated with calcium gluconate, cefotaxime, ciprofloxacin, glucose, insulin, midazolam, sodium bicarbonate, terlipressin, amino acids, meropenem, paracetamol, and potassium. On 03 Feb 2015 (Day 384), bile duct obstruction improved to Grade 2. On 04 Feb 2015 (Day 385), the subject recovered from hyperkalemia. On 12 Feb 2015 (Day 393), the subject recovered from acute kidney injury. On 17 Feb 2015 (Day 398), the subject was withdrawn from the study due to bile duct obstruction and received the last dose on 01 Feb 2015 (Day 382). On 09 Mar 2015 (Day 418), the subject recovered from bile duct obstruction. The Investigator considered bile duct obstruction and acute kidney injury serious and not related to the study drug; hyperkalemia nonserious and not related to the study drug.

On 08 May 2015 (Day 478), tumor response assessment showed disease progression.

On 10 Sep 2015 (Day 603, 221 days after the last dose), the subject died due to disease progression.

Subject Number	30061010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004096
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Decreased appetite, Metastases to spine

A 62-year-old Asian female was diagnosed with hepatocellular carcinoma on 08 Jul 2008. Significant medical history included benign neoplasm of thyroid gland, chronic hepatitis B, periodontitis, gastric varices, hepatic cyst, hepatic cirrhosis, emphysema, intervertebral disc protrusion, and toothache. Previous anticancer therapies included high frequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included acetylcysteine, amlodipine, candesartan, cimetropium, entecavir, flumazenil, furosemide, hepatamine, human albumin, hyaluronic acid, ketorolac, lactulose, levofloxacin, megestrol, midazolam, mupirocin, mydrin p, oxycodone, pancreatin, paracetamol, pethidine, pronase, quetiapine, rifaximin, simeticone, smoflipid, spironolactone, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed at right upper lobe lung mass and MRI showed right lobe liver lesion. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 24 Oct 2014 (Day 1), treatment with study drug was initiated.

On 05 Jan 2015 (Day 74), the subject experienced decreased appetite (Grade 2). On 12 Feb 2015 (Day 112), the subject was hospitalized for worsening of decreased appetite (Grade 3). Treatment included megestrol, hepatamine, and smoflipid. On 13 Feb 2015 (Day 113), the study drug was interrupted due to decreased appetite. On 05 Mar 2015 (Day 133), the subject recovered from decreased appetite. The Investigator considered decreased appetite serious and possibly related to the study drug.

On 12 Feb 2015 (Day 112), tumor response assessment showed disease progression. The subject received the last dose of the study drug on 12 Feb 2015 (Day 112). On 02 Mar 2015 (Day 130), the subject was withdrawn from the study due to disease progression.

On 09 Mar 2015 (Day 137), the subject was hospitalized for metastases to spine (Grade 3). Bone scan showed new active bone lesion in lower C-spine, T11, L3-4, left iliac bone, and left parietal bone. CT scan confirmed metastatic spine lesion. On 25 Mar 2015 (Day 153), the subject was treated with palliative radiotherapy and was also treated with fentanyl patch and pethidine. The subject did not recover from metastases to spine. The Investigator considered metastases to spine serious and not related to the study drug but related to disease progression.

On 11 Apr 2015 (Day 170, 58 days after the last dose), the subject died due to disease progression. Autopsy was not performed.

Subject Number	30061011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006364
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Groin abscess

A 76-year-old Asian male was diagnosed with hepatocellular carcinoma on 04 Feb 2014. Significant medical history included abdominal pain, decreased appetite, polyarthritis (arthritis on shoulders, knee, and ankles), asthma, cholelithiasis, hypertension, laryngitis, alcoholic cirrhosis, back pain, spinal osteoarthritis, pancreatitis, emphysema, and spinal column stenosis. Previous anticancer therapies included transcatheter arterial chemoembolization and radioembolization. Prior and concomitant medications included ambroxol, amlodipine, biosol, bisacodyl, cefotaxime, chlorhexidine, ciprofloxacin, cimetropium, diosmectite, flumazenil, furosemide, glycopyrronium, hepatamine, human albumin, ketorolac, lactobacillus acidophilus, lactec, lansoprazole, lidocaine, megestrol, metoclopramide, metronidazole, midazolam, mosapride, nefopam, neoamiyu, oxycodone, palonosetron, pancreatin, pantoprazole, paracetamol, pethidine, potassium, pronase, propacetamol, propofol, pyridostigmine, remifentanil, rifaximin, rocuronium, simeticone, smoflipid, spironolactone, targin, transipeg, unacid, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at quadrate and right liver lobes; masses at right lower and middle lung lobes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 07 Apr 2015 (Day 111), the subject experienced inguinal hernia (Grade 2). On 21 Apr 2015 (Day 125), the study drug was interrupted due to inguinal hernia, and on the same day (Day 125), the subject also experienced increased C-reactive protein (Grade 2) with CRP 64.9 mg/L (NR: 0 – 5). On 24 Apr 2015 (Day 128), the subject was hospitalized for groin abscess (right inguinal; Grade 3). The CT scan of the abdomen showed interval increase in extent of lipiodol containing fluid collection at the retroperitoneum resulting in lumbar hernia, inguinal hernia, and secondary infection at scrotum. The subject was treated with ciprofloxacin, unacid, cefotaxime, and metronidazole. On 27 Apr 2015 (Day 131), the subject underwent pig tail catheter placement for the abscess to drain. On 06 May 2015 (Day 140), the subject underwent incisional drainage and the subject was treated with ambroxol, glycopyrronium, ketorolac, lidocaine, nefopam, oxycodone, palonosetron, pantoprazole, propofol, pyridostigmine, and rocuronium. On the same day (Day 140), the subject recovered from inguinal hernia. On 27 May 2015 (Day 161), the subject experienced groin pain (Grade 2) and on 28 May 2015 (Day 162), the subject experienced pyrexia (Grade 1). On 28 May 2015 (Day 162), the subject recovered from pyrexia. On 14 Jun 2015 (Day 179), the subject recovered from groin pain. On 24 Jun 2015 (Day 189), the subject recovered from groin abscess. The subject did not recover from increased C-reactive protein. The Investigator considered groin abscess serious and not related to the study drug; inguinal hernia, groin pain, increased C-reactive protein, and pyrexia nonserious and not related to the study drug.

On 01 Jun 2015 (Day 166), tumor response assessment showed disease progression. On 09 Jun 2015 (Day 174), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 20 Apr 2015 (Day 124).

On 30 Jul 2015 (Day 225, 101 days after the last dose), the subject died due to disease progression.

Subject Number	30071006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005429
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diarrhoea

A 50-year-old Asian male was diagnosed with hepatocellular carcinoma in Feb 2013. Significant medical history included erosive gastritis, esophageal varices, hepatic cirrhosis, and hepatitis B. Previous anticancer therapies included radiotherapy to para-caval lymph node, hepatic intra-arterial chemotherapy, and transcatheter arterial chemoembolization. Prior and concomitant medications included allopurinol, bisacodyl, domperidone, hydrocortisone, lansoprazole, loperamide, loxoprofen, midazolam, movicol, pantoprazole, pinaverium, prednisolone, streptokinase, tenofovir, and tiropramide. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe and para-caval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 01 Sep 2014 (Day 242), the subject experienced diarrhea (Grade 1) and the subject was treated with loperamide and pinaverium. The diarrhea persisted and on 02 Mar 2015 (Day 424), the subject was hospitalized for worsening diarrhea (Grade 3) and loperamide and pinaverium were continued. On 14 Mar 2015 (Day 436), the subject recovered from diarrhea. The Investigator considered diarrhea serious and possibly related to the study drug.

On 25 Mar 2015 (Day 447), the subject experienced diarrhea (Grade 1). On 27 Mar 2015 (Day 449), the study drug dose was reduced to 8 mg/day due to diarrhea. On 21 May 2015 (Day 504), the subject recovered from diarrhea. The Investigator considered diarrhea nonserious and possibly related to the study drug.

On 25 Feb 2016 (Day 784), tumor response assessment showed disease progression. On 26 Feb 2016 (Day 785), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 25 Feb 2016 (Day 784).

Subject Number	30071009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002427
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Decreased appetite, Ascites

A 40-year-old Asian male was diagnosed with hepatocellular carcinoma on 13 Mar 2014. Significant medical history included diabetes mellitus, hepatitis B, hepatic cirrhosis, recurrent duodenal ulcer, gastroesophageal reflux disease, and seborrheic dermatitis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included celecoxib, gemigliptin, glimepiride, granisetron, hepatamine, hydrocortisone, lactulose, lithium, loperamide, metformin, metoclopramide, minerals w/vitamins, morphine, pangest f, pantoprazole, prednicarbate, pregabalin, rabeprazole, silybum marianum, sucralfate, telbivudine, tiropramide, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at quadrate lobe of liver, tumor thrombus in left portal vein; lymphadenopathy at celiac axis, and multiple lymph node metastases. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 01 Dec 2014 (Day 243), the subject was hospitalized for decreased appetite (Grade 3). On 10 Dec 2014 (Day 252), the study drug was interrupted due to decreased appetite and the subject was treated with granisetron and metoclopramide. On the same day (Day 252), the subject experienced decreased weight (Grade 2) with weight of 58.6 kg (Baseline: 77.5 kg). On 15 Dec 2014 (Day 257), the severity of decreased appetite improved to Grade 2 and the subject was discharged from the hospital. The study drug was resumed at reduced dose of 8 mg/day due to decreased appetite. The subject did not recover from decreased appetite and decreased weight. The Investigator considered decreased appetite serious and possibly related to study drug; decreased weight nonserious and possibly related to study drug.

On 09 Jan 2015 (Day 282), tumor response assessment showed disease progression. On 13 Jan 2015 (Day 286), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 12 Jan 2015 (Day 285). The subject commenced new anticancer treatment following discontinuation of the study drug.

On 28 May 2014 (Day 56), the subject experienced ascites (Grade 1). On 18 Jan 2015 (Day 291), the event worsened to Grade 3. On 20 Jan 2015 (Day 293), the subject underwent paracentesis in the emergency room, which drained 1400 cc fluid and ascites improved to Grade 2 on the same day (Day 293). Fluid analysis was negative for malignant cell. The subject was treated with furosemide and spironolactone. On 20 Jan 2015 (Day 293), the subject was discharged from the emergency room. The subject did not recover from ascites. The Investigator considered ascites serious (important medical event) and possibly related to study drug.

On 14 Apr 2015 (Day 377, 92 days after the last dose), the subject died due to disease progression.

Subject Number	30071012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010747
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Biliary dilatation, Ascites, Blood bilirubin increased

A 53-year-old Asian male was diagnosed with hepatocellular carcinoma in Dec 2009. Significant medical history included abdominal pain, acquired intra hepatic duct dilatation, adjustment disorder, back pain, erosive gastritis, hepatitis B, and bone metastasis (T9, T10, T11, and L2). Previous anticancer therapies included radiotherapy to T spine 7 to 12, heat therapy, hepatectomy (2x), high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included, alprazolam, amlodipine, bisacodyl, buspirone, cefixime, cefotaxime, chlorhexidine, clobetasol, diosmectite, entecavir, escitalopram, famotidine, fentanyl, furosemide, general nutrients, glucose, granisetron, hepatamine, human albumin, human insulin, hydrocortisone, hydromorphone, hyoscine, itopride, lactulose, lorazepam, magnesium hydroxide, magnesium oxide, megestrol, meropenem, metoclopramide, midazolam, mirtazapine, morphine, mupirocin, other therapeutic products, oxycodone, pancreatin, pangest f, pantoprazole, pethidine, piroxicam, pregabalin, protein supplements, rabeprazole, rifaximin, silybum marianum, spironolactone, tramadol, triazolam, ultracet, ursodeoxycholic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at multifocal right liver lobe, bone metastases, right lung mass, lesion invading the diaphragmatic area, and lung metastases. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 23 Sep 2014 (Day 83), the subject experienced hypertension (Grade 3) with blood pressure of 160/93 mmHg. The subject was treated with amlodipine and the study drug was interrupted. On 25 Sep 2014 (Day 85), severity of hypertension improved to Grade 1 with blood pressure of 134/79 mmHg and the study drug was resumed at a reduced dose of 8 mg/day due to hypertension. On 18 Dec 2014 (Day 169), the subject recovered from hypertension with blood pressure of 117/70 mmHg. The Investigator considered hypertension nonserious and possibly related to the study drug.

On 27 Jul 2015 (Day 390), the subject experienced increased biliary dilatation (Grade 3). Computerized tomography scan of liver showed new bile duct dilation. Laboratory tests showed ALP 153 U/L (NR: 43 – 115), AST 60 U/L (NR: 10 – 43), and total bilirubin 31.1 umol/L (NR: 0 – 18.8). On 22 Sep 2015 (Day 447), repeat laboratory tests showed albumin 34 g/L (NR: 35 – 55), AST 89 U/L, total bilirubin 44.5 umol/L, ALP 200 U/L, GGT 88 U/L (NR: 10 – 49) and creatinine 44 umol/L (NR: 62 – 124). On 24 Sep 2015 (Day 449), the subject was hospitalized for persistent increased biliary dilatation. Magnetic resonance imaging of liver showed increased bile duct dilatation by duct stricture without obstructive mass and a liver dynamic enhanced CT scan showed increased bile duct dilatation by

duct stricture and bland thrombus in main portal vein. On 25 Sep 2015 (Day 450), the subject underwent endoscopic nasobiliary drainage. On the same day (Day 450), the subject experienced cholelithiasis (Grade 1). The laboratory tests showed AST 121 U/L (NR: 0 – 40), total bilirubin 58.14 umol/L (NR: 3.42 – 20.52), and albumin 34 g/L (NR: 33 – 52). On 26 Sep 2015 (Day 451), the study drug was interrupted due to increased biliary dilatation. On 30 Sep 2015 (Day 455), fluoroscopy of bile duct was performed; endoscopic nasobiliary drainage was removed and endoscopic retrograde biliary drainage stent was inserted through endoscopic retrograde cholangiopancreatography. On 30 Sep 2015 (Day 455), the subject experienced pyrexia (Grade 1) with body temperature of 38.8 °C. The subject was treated with cefotaxime. On 03 Oct 2015 (Day 458), the subject experienced hypoalbuminemia (Grade 2) with albumin of 28 g/L (NR: 33 – 52) and was treated with human albumin. On 06 Oct 2015 (Day 461), ultrasound of the liver, gallbladder, biliary tract, and spleen showed a decreased extent of bile duct dilatation in the left lobe. On the same day (Day 461), the subject recovered from hypoalbuminemia with albumin of 30 g/L (NR: 33 – 52). On 07 Oct 2015 (Day 462), severity of increased biliary dilatation improved to Grade 2 and the subject was discharged from the hospital. On 14 Oct 2015 (Day 469), the subject recovered from pyrexia. The subject did not recover from cholelithiasis and biliary dilatation. The Investigator considered biliary dilatation serious and not related to the study drug; cholelithiasis, hypoalbuminemia, and pyrexia nonserious and not related to the study drug.

On 20 Oct 2015 (Day 475), the subject was again hospitalized for worsening of biliary dilatation (Grade 3). Laboratory tests showed albumin 27 g/L (NR: 35 – 55), AST 61 U/L (NR: 10 – 43), ALP 250 U/L, creatinine 35 umol/L, and total bilirubin 54 umol/L (NR: 0 – 18.8). The subject also experienced pyrexia (Grade 1) with body temperature of 38.6 °C. Blood culture showed negative results. The subject was treated with cefotaxime. On 21 Oct 2015 (Day 476), the study drug was resumed at the same dose. On 27 Oct 2015 (Day 482), the subject recovered from pyrexia. On 29 Oct 2015 (Day 484), severity of biliary dilatation improved to Grade 2 and the subject was discharged from the hospital. The subject did not recover from biliary dilatation. The Investigator considered biliary dilatation serious and not related to the study drug; pyrexia nonserious and not related to the study drug.

On 17 Nov 2015 (Day 503), the subject was hospitalized for ascites (Grade 3) which was ongoing since 26 Aug 2014 (Day 55) as Grade 1. The subject underwent multiple paracentesis and was also treated with spironolactone and human albumin. On 19 Nov 2015 (Day 505), the subject experienced biliary dilatation (Grade 2) which further prolonged hospitalization. On the same day (Day 505), the study drug was interrupted due to ascites and biliary dilatation. Laboratory tests showed absolute neutrophils 8.4 x10^9/L (NR: 1.7 – 7.9), albumin 22 g/L (NR: 35 – 55), ALP 191 U/L, ALT 7 U/L (NR: 10 – 40), AST 46 U/L (NR: 10 – 43), total bilirubin 47.4 umol/L (NR: 0 – 18.8), sodium 129 mmol/L (NR 133 – 145), and creatinine 35 umol/L. On 26 Nov 2015 (Day 512), blood culture showed spontaneous bacterial peritonitis (Grade 1) and the subject was treated with meropenem. On 04 Dec 2015 (Day 520), CT scan of liver showed decreased ascites. On 12 Dec 2015 (Day 528), the subject recovered from spontaneous bacterial peritonitis. On 14 Dec 2015 (Day 530), severity of ascites improved to Grade 1. On 15 Dec 2015 (Day 531), the study drug was resumed at a reduced dose of 4 mg/day due to ascites. On 11 Feb 2016 (Day 589), the subject recovered from ascites. The subject did not recover from biliary dilatation. The Investigator considered ascites serious and

probably related to the study drug; biliary dilatation serious and not related to the study drug; spontaneous bacterial peritonitis nonserious and not related to the study drug.

On 06 Jan 2016 (Day 553), the subject experienced constipation (Grade 2) and was treated with bisacodyl. On 14 Jan 2016 (Day 561), the study drug was interrupted due to constipation. On 15 Jan 2016 (Day 562), severity of constipation improved to Grade 1. On 16 Jan 2016 (Day 563), the study drug was resumed at a reduced frequency of 4 mg every other day due to this event. The subject did not recover from constipation. The Investigator considered constipation nonserious and possibly related to the study drug.

On 11 Feb 2016 (Day 589), the subject was hospitalized for increased blood bilirubin (Grade 3) with total bilirubin of 78.66 umol/L (NR: 3.42 – 20.52). The subject also experienced hypoalbuminemia (Grade 1) with albumin of 34 g/L (NR: 35 – 55). On the same day, the study drug was interrupted due to increased blood bilirubin. The subject was treated with human albumin. The subject did not recover from increased blood bilirubin and hypoalbuminemia. The Investigator considered increased blood bilirubin serious and possibly related to the study drug; hypoalbuminemia nonserious and not related to the study drug.

On 08 Mar 2016 (Day 615), tumor response assessment showed disease progression. On 09 Mar 2016 (Day 616), the subject was withdrawn from study due to disease progression and received the last dose of the study drug on 10 Feb 2016 (Day 588).

On 06 Jul 2016 (Day 735, 147 days after the last dose), the subject died due to unknown reason.

Subject Number	30071013
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-002967
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Ascites

A 47-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Apr 2014. Significant medical history included abdominal pain, constipation, and hepatitis B. Previous anticancer therapies included radiotherapy to mass in right lobe of liver and transcatheter arterial chemoembolization. Prior and concomitant medications included bisacodyl, celecoxib, famotidine, fentanyl, furosemide, granisetron, human albumin, hydromorphone, lactulose, magnesium hydroxide, megestrol, metoclopramide, morphine, rabeprazole, silybum marianum, spironolactone, tamsulosin, telbivudine, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe of liver, multifocal infiltrative HCC, tumor peritoneal seedings (pelvic cavity), and tumor thrombus in right lobe of liver; lung mass multiple metastases in right lower lobe and left lobe of lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 24 Jul 2014 (Day 1), treatment with study drug was initiated.

On 10 Aug 2014 (Day 18), the subject experienced nausea (Grade 1). Treatment included granisetron, megestrol, and metoclopramide. On 27 Aug 2014 (Day 35), the severity of nausea worsened to Grade 2. On 02 Sep 2014 (Day 41), the study drug was reduced to 8 mg/day due to nausea. On 14 Oct 2014 (Day 83), nausea improved to Grade 1. On 01 Feb 2015 (Day 193), the subject recovered from nausea. The Investigator considered nausea nonserious and possibly related to study drug.

On 17 Dec 2014 (Day 147), the subject experienced ascites (Grade 3). Due to its persistence, the subject was hospitalized on 07 Jan 2015 (Day 168). Laboratory tests showed albumin 33 g/L (NR: 33 – 52), AST 69 U/L (NR: 0 – 40), ALT 15 U/L (NR: 0 – 40), and total bilirubin 20.52 umol/L (NR: 3.42 – 20.52). On 07 Jan 2015 (Day 168), the subject underwent abdominal paracentesis and 1600 cc fluid was drained and cytology tests were negative for malignancy. Treatment included human albumin, furosemide, and spironolactone. On 08 Jan 2015 (Day 169), the study drug was interrupted due to ascites. On 13 Jan 2015 (Day 174), the subject was discharged from the hospital. On 26 Jan 2015 (Day 187), the subject underwent paracentesis and 3200 cc fluid was drained. The subject did not recover from ascites. The Investigator considered ascites serious and possibly related to the study drug.

On 02 Feb 2015 (Day 194), the subject was withdrawn from the study due to clinical disease progression and received the last dose on 07 Jan 2015 (Day 168).

On 22 Apr 2015 (Day 273, 105 days after the last dose), the subject died due to unknown cause.

Subject Number	30071016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-013995
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Metastases to central nervous system
AE(s) Leading to Discontinuation	Metastases to central nervous system

A 54-year-old Asian male was diagnosed with hepatocellular carcinoma in Sep 2011. Significant medical history included chronic gastritis, diabetes mellitus, hepatitis B, hyperlipidemia, hypertension, and diabetic retinopathy. Previous anticancer therapies included transcatheter arterial chemoembolization and hepatectomy. Prior and concomitant medications included amlodipine, atorvastatin, cebetabs, celecoxib, chlorhexidine, clobetasol, dexamethasone, famotidine, hepatamine, human insulin, hydrochlorothiazide, insulin glargine, joins, lafutidine, linagliptin, megestrol, metformin, midazolam, mupirocin, optiderm, rabeprazole, silybum marianum, thioctic acid, ursodeoxycholic acid, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, metastases at bilateral lungs, tumor thrombus in MHV to IVC, and bilateral lower lung lobe masses. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 23 Oct 2014 (Day 1), treatment with study drug was initiated.

On 27 Jul 2015 (Day 278), the subject experienced diarrhea (Grade 2). On 30 Jul 2015 (Day 281), the severity of diarrhea improved to Grade 1. The subject was treated with hepatamine. On the same day (Day 281), the dose of the study drug was reduced to 8 mg/day due to this event. On 25 Aug 2015 (Day 307), the subject recovered from diarrhea. The Investigator considered diarrhea nonserious and possibly related to the study drug.

On 22 Jan 2016 (Day 457), the subject was hospitalized for metastases to central nervous system (Grade 3). The CT scan of brain showed multiple hemorrhagic brain metastases in left posterior temporal lobe, both occipital lobes, and left parietal lobe. The subject was treated with dexamethasone, rabeprazole, and radiotherapy. On 27 Jan 2016 (Day 462), tumor response assessment showed disease progression. On the same day (Day 462), the study drug was withdrawn due to this event. On 28 Jan 2016 (Day 463), the subject was withdrawn from the study due to metastases to central nervous system secondary to disease progression and the subject received the last dose of the study drug on 26 Jan 2016 (Day 461). The subject did not recover from metastasis to central nervous system. The Investigator considered metastases to central nervous system serious and not related to the study drug but related to disease progression.

On 10 May 2016 (Day 566, 105 days after the last dose), the subject died due to unknown reason.

Subject Number	30091011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01444-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diarrhoea

A 60-year-old Asian male was diagnosed with hepatocellular carcinoma on 09 Nov 2012. Significant medical history included cholecystectomy, hepatitis B, hypertension, and hepatic cirrhosis. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included alverine, amlodipine, benzydamine, bromhexine, corydalis yanhusuo tuber w/ipomoea nil seed, cough and cold preparations, diosmectite, glycine, levocloperastine, levodropropizine, loperamide, megestrol, menatetrenone, metoclopramide, sodium bicarbonate, streptokinase, tiotropium, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right lobes of liver, right lower lobe and multiple lung masses, and hepatoduodenal ligament lymphadenopathies. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 24 Jan 2014 (Day 29), the subject experienced proteinuria (Grade 1) with urine protein dipstick 3+. The study drug was interrupted due to this event. On 26 Jan 2014 (Day 31), laboratory tests showed 24h urine protein 0.9316 g/24hr. On 30 Jan 2014 (Day 35), the subject experienced diarrhea (Grade 1). On the same day (Day 35), the study drug was resumed at the same dose. On 03 Feb 2014 (Day 39), the severity of diarrhea worsened to Grade 3. On 04 Feb 2014 (Day 40), the subject was hospitalized for diarrhea and also experienced dyspnea (Grade 2). On the same day (Day 40), the study drug was interrupted due to diarrhea. Treatment included tiotropium, diosmectite, and loperamide. The severity of diarrhea improved to Grade 1. On 06 Feb 2014 (Day 42), the subject experienced abdominal pain (Grade 1). Treatment included tramadol. The subject recovered on the same day. On 08 Feb 2014 (Day 44), the subject recovered from diarrhea and was discharged from the hospital. On 10 Feb 2014 (Day 46), the subject recovered from proteinuria with urine protein dipstick 1+. On the same day (Day 46), the study drug was resumed at reduced dose of 8 mg/day due to diarrhea. On 16 Feb 2014 (Day 52), severity of dyspnea worsened to Grade 3 and the study drug was interrupted on the same day. On 17 Feb 2014 (Day 53), tumor response assessment showed disease progression. On 18 Feb 2014 (Day 54), severity of dyspnea improved to Grade 2. On the same day (Day 54), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 16 Feb 2014 (Day 52). The subject did not recover from dyspnea. The Investigator considered diarrhea serious and possibly related to study drug; proteinuria nonserious and probably related to study drug; abdominal pain and dyspnea nonserious and not related to study drug.

On 17 May 2014 (Day 142, 90 days after the last dose), the subject died due to disease progression.