On 17 Jul 2014 (Day 161, 105 days after the last dose), the subject died due to disease progression.

Subject Number	12131004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01388-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy, Ascites

A 71-year-old Japanese male was diagnosed with hepatocellular carcinoma on 29 Jul 2013. Significant medical history included chronic gastritis, diabetes mellitus, hypertension, hepatic cirrhosis, and splenomegaly. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included acetylcysteine, alogliptin, aminoleban, amlodipine, antibiotic-resistant lactic acid bacteriae (enteronon-R), ascorbic acid, azilsartan, bacteria w/hydrocortisone, beclometasone, bifidobacterium lactis, bio-three, brotizolam, canrenoic acid, carbohydrates w/potassium chloride/sodium, clobetasol, dequalinium, dextrose and sodium chloride injection, diclofenac, falkamin, felbinac, furosemide, human albumin, hydrocortison med terramycin, hydroxyzine, influenza vaccine, insulin aspart, kanamycin, ketoprofen, lactulose, levocarnitine, levothyroxine, loperamide, loxoprofen, menatetrenone, meropenem, metformin, neurobion, pa (PL for common cold), paracetamol, piperacillin/tazobactam, rabeprazole, rebamipide, shakuyakukanzoto, sodium chloride, solita-t1, spironolactone, tolvaptan, urea, voglibose, white soft paraffin, zinc, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver and para-caval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 05 Sep 2013 (Day 8), the subject experienced hepatic encephalopathy (Grade 2) and was treated with lactulose. On 12 Sep 2013 (Day 15), the subject experienced proteinuria (Grade 2) with urine protein of 4+. On 17 Oct 2013 (Day 50), the subject experienced ascites (Grade 2) and hepatic edema (Grade 2). CT scan of abdomen showed ascites. Treatment included furosemide and spironolactone. On 23 Oct 2013 (Day 56), the subject was hospitalized for worsening hepatic encephalopathy (Grade 3) with symptoms of disorientation and fecal incontinence. The subject also experienced hypoalbuminemia (Grade 2). The study drug was interrupted due to hepatic encephalopathy, ascites, and hepatic edema. Laboratory tests showed ammonia 97 umol/L (NR: 11 – 32) and albumin 29 g/L (NR: 38 – 50). Treatment included bio-three, aminoleban, kanamycin, lactulose, and human albumin. On 24 Oct 2013 (Day 57), the severity of proteinuria improved to Grade 1 with urine protein of 1+. On 26 Oct 2013 (Day 59), the severity of hepatic encephalopathy improved to Grade 1. On 05 Nov 2013 (Day 69), the severity of hypoalbuminemia improved to Grade 1 with albumin 30 g/L and on 06 Nov 2013 (Day 70), the severity of hepatic edema improved to Grade 1 and on 07 Nov 2013 (Day 71), ascites (unspecified) improved to Grade 1. On 13 Nov 2013 (Day 77), the study drug was resumed at reduced dose of 8 mg/day due to hepatic edema and ascites. On 19 Nov 2013 (Day 83), the subject recovered from hypoalbuminemia. On 23 Nov 2013 (Day 87), the subject was discharged from the hospital. On 02 Dec 2013 (Day 96), the subject recovered from proteinuria. On 12 Dec 2013 (Day 106), the subject recovered from ascites and CT scan

showed the absence of ascites. The subject did not recover from hepatic encephalopathy and hepatic edema. The Investigator considered hepatic encephalopathy serious and not related to study drug; hepatic edema, hypoalbuminemia, and ascites nonserious and possibly related to study drug; proteinuria nonserious and probably related to study drug.

On 20 Feb 2014 (Day 176), the subject experienced diarrhea (Grade 2) and on 10 Mar 2014 (Day 194), the severity of diarrhea increased to Grade 3. The subject was treated with bifidobacterium lactis and loperamide. On 11 Mar 2014 (Day 195), the study drug was interrupted due to diarrhea. On 13 Mar 2014 (Day 197), the subject recovered from diarrhea and the study drug was resumed at reduced dose of 4 mg/day due to this event. The Investigator considered diarrhea nonserious and possibly related to study drug.

On 29 Mar 2014 (Day 213), the subject was hospitalized for worsening of ascites (Grade 3) which was ongoing since 17 Jan 2014 (Day 142) as Grade 2. The study drug was interrupted and the subject was treated with spironolactone, furosemide, canrenoic acid, and tolvaptan. On 03 Apr 2014 (Day 218), tumor response assessment showed disease progression. On 04 Apr 2014 (Day 219), the subject experienced hypoalbuminemia (Grade 2) with albumin 29 g/L. The subject underwent ascites drainage and ascites reinfusion therapy. On 09 Apr 2014 (Day 224), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 28 Mar 2014 (Day 212). The subject did not recover from ascites and hypoalbuminemia. The Investigator considered ascites serious and possibly related to study drug; hypoalbuminemia nonserious and not related to study drug.

On 08 Aug 2014 (Day 345, 133 days after the last dose), the subject died due to disease progression.

Subject Number	12141003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01507-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Blood bilirubin increased
AE(s) Leading to Discontinuation	Blood bilirubin increased, Hepatic function abnormal, Fatigue

A 77-year-old Japanese male was diagnosed with hepatocellular carcinoma on 16 May 2013. Significant medical history included chronic gastritis, large intestine polyp, hepatic cirrhosis, insomnia, pruritus, and musculoskeletal pain (right shoulder pain). Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/electrolytes/glucose/thiamine (Bfluid), amino acids w/vitamins, amlodipine, asphagen, betamethasone, brotizolam, diclofenac, diphenhydramine, epinastine, falkamin, furosemide, gentamicin, glucose, influenza vaccine, juzentaihoto, l-carbocysteine, levothyroxine, loxoprofen, magnesium oxide, menatetrenone, misoprostol, neurobion, nutrients, osmosal, solita-t1, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right and left lobe of liver and right rib mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 18 Mar 2014 (Day 264), the subject experienced decreased appetite (Grade 2). Treatment included amino acids w/vitamins, nutrients, betamethasone, and juzentaihoto. The study drug dose did not change. The subject did not recover from this event. The Investigator considered decreased appetite nonserious and probably related to study drug.

On 01 Apr 2014 (Day 278), the subject experienced decreased weight (Grade 2) with weight loss of 6.4 kg (Baseline: 54.1 kg). The study drug dose did not change. The subject did not recover. The Investigator considered decreased weight nonserious and probably related to study drug.

On 13 May 2014 (Day 320), the subject experienced increased blood bilirubin (Grade 3) and the study drug was interrupted on the same day due to this event. Laboratory tests showed total bilirubin 63.27 umol/L (NR: 3.42 – 17.1). Abdominal ultrasound showed no bile duct obstruction. On 20 May 2014 (Day 327), the subject experienced fatigue (Grade 2). On 21 May 2014 (Day 328), the subject was hospitalized for increased blood bilirubin. The severity of decreased appetite and decreased weight worsened to Grade 3. Treatment included glucose, amino acids w/electrolytes/glucose/thiamine (Bfluid), neurobion, menatetrenone, asphagen, and osmosal. The study drug remained interrupted due to decreased weight and decreased appetite. On 27 May 2014 (Day 334), the severity of increased blood bilirubin improved to Grade 2 and the subject experienced abnormal hepatic function (Grade 3), and ascites (unspecified; Grade 1). Abdominal CT scan showed ascites. Laboratory tests on 30 May 2014 (Day 337) showed albumin 24 g/L (NR: 35 – 55), ALP 405 U/L (NR: 43 – 115), ALT 390 U/L (NR: 10 – 40), AST 356 U/L (NR: 10 – 43), and total bilirubin of 27.7 umol/L

(NR: 1.7 – 18.8). On 31 May 2014 (Day 338), the subject was discharged from the hospital. The subject did not recover from increased blood bilirubin, abnormal hepatic function, ascites, fatigue, decreased appetite, and decreased weight. On 10 Jun 2014 (Day 348), the study drug was withdrawn due to fatigue. On the same day (Day 348), the subject was withdrawn from the study due to clinical disease progression and received the last dose of study drug on 12 May 2014 (Day 319). The Investigator considered increased blood bilirubin serious and not related to study drug but related to disease progression; decreased appetite and decreased weight nonserious and probably related to study drug; abnormal hepatic function, ascites, fatigue nonserious and not related to study drug but related to disease progression.

On 15 Jun 2014 (Day 353, 34 days after the last dose), the subject died due to clinical disease progression.

Subject Number	12141020
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-005122
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Pneumonia, Paralysis recurrent laryngeal nerve

A 77-year-old Japanese male was diagnosed with hepatocellular carcinoma on 21 Aug 2014. Significant medical history included acute hepatitis, duodenal ulcer, gastritis, alcoholic cirrhosis, hypertension, hyperuricemia, and lumbar spinal stenosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included alclometasone, allopurinol, ambroxol, amino acids w/electrolytes/glucose/thiamine, amlodipine, benproperine, bepotastine, betamethasone, carbohydrates w/potassium chloride/sodium, cefazolin, cefcapene, cefditoren, clarithromycin, dexamethasone, difluprednate, diphenhydramine, ecabet, eperisone, esomeprazole, famotidine, febuxostat, furosemide, gentamicin, glycerol, gualenic acid, heparinoid, hyoscine, l-carbocysteine, levofloxacin, levothyroxine, lidocaine, limaprost, lisinopril, magnesium oxide, mecobalamin, nalfurafine, nutrients (ensure liquid), pa, pabron s gold, paracetamol, pronase, pueraria montana, salicylic acid, sitafloxacin, theophylline, tiotropium, tizanidine, tramadol, trichlormethiazide, tulobuterol, unacid, urea, valisone-g, white soft paraffin, and zinc. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 13 Mar 2015 (Day 183), the subject experienced pneumonia (Grade 2) with symptoms of difficulty in breathing, cough, and sputum production. Treatment included ambroxol, benproperine, sitafloxacin, and tulobuterol. Due to its persistence, the subject was hospitalized on 19 Mar 2015 (Day 189) for pneumonia (Grade 3) which was confirmed via chest CT scan. Treatment included clarithromycin, theophylline, tiotropium, and unacid. On 29 Mar 2015 (Day 199), the subject experienced recurrent laryngeal nerve paralysis (Grade 2). On 07 Apr 2015 (Day 208), the subject recovered from pneumonia. On 07 Apr 2015 (Day 208), the recurrent laryngeal nerve paralysis worsened to Grade 3. Chest and cervical CT scan was unable to identify the cause of recurrent laryngeal nerve paralysis. On 07 Apr 2015 (Day 208), the subject underwent tracheostomy and tracheal cannula insertion. Treatment included cefazolin, amino acids w/electrolytes/glucose/thiamine, lidocaine, betamethasone, and gentamicin. On 08 Apr 2015 (Day 209), the study drug was interrupted due to this event. On 15 Apr 2015 (Day 216), the study drug was resumed at same dose. On 23 Apr 2015 (Day 224), the subject was discharged from the hospital. The subject did not recover from recurrent laryngeal nerve paralysis. The Investigator considered pneumonia and recurrent laryngeal nerve paralysis serious and not related to study drug.

On 17 Sep 2015 (Day 371), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 3) which started on 28 Jul 2015 (Day 320) as Grade 2. The study drug was interrupted due to the event. The subject was treated with heparinoid, difluprednate, gentamicin, salicylic

acid, betamethasone, and white soft paraffin. On 07 Oct 2015 (Day 391), the study drug was resumed at reduced dose of 8 mg/day due to the event. On 09 Aug 2016 (Day 698), the subject recovered from the event. The Investigator considered the event nonserious and probably related to the study drug.

On 07 Jun 2016 (Day 635), the study drug was reduced to 4 mg/day due to proteinuria (Grade 2) which was persistent since 24 Mar 2015 (Day 194) as Grade 1. The subject did not recover from proteinuria. The Investigator considered proteinuria nonserious and probably related to the study drug.

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

Subject Number	12191009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01561-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cancer pain

A 42-year-old Japanese male was diagnosed with hepatocellular carcinoma on 14 Jan 2014. Significant medical history included cancer pain, gastritis, large intestine polyp, and non-alcoholic fatty liver. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, denosumab, dimeticone, domperidone, esomeprazole, faropenem, fentanyl, imipramine, l-carbocysteine, lidocaine, loxoprofen, lysozyme, magnesium oxide, oxycodone, polaprezinc, prochlorperazine, pronase, sennoside a+b, shosaikotokakikyosekko, sitafloxacin, sodium bicarbonate, super cal, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right lobes of liver, masses at omentum, lumbar vertebra and left lower lobe and right middle lobe of lung; and porta-hepatis lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 09 Apr 2014 (Day –7), the subject experienced worsening of cancer pain (Grade 2) and was treated with palliative radiotherapy to lumbosacral spine on 28 Apr 2014 (Day 13) until 02 May 2014 (Day 17). On 05 May 2014 (Day 20), the subject was hospitalized for worsening of cancer pain (Grade 3). Treatment included fentanyl, oxycodone, and imipramine. From 09 May 2014 (Day 24) until 15 May 2014 (Day 30), the subject received radiation therapy for pain relief (C6 to Th3). The subject was recovering from worsening of cancer pain. The Investigator considered worsening of cancer pain serious and not related to study drug but related to disease progression.

On 30 Jul 2014 (Day 106), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression. The subject received the last dose on same day (Day 106).

On 20 Nov 2014 (Day 219, 113 days after the last dose), the subject died due to disease progression.

Subject Number	12201002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007903
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Spinal compression fracture, Hepatic failure
AE(s) Leading to Discontinuation	Hepatic failure

A 63-year-old Japanese male was diagnosed with hepatocellular carcinoma on 05 Jun 2012. Significant medical history included chronic hepatitis C, esophageal varices, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/electrolytes/glucose/thiamine (B Fluid), aminoleban en, amlodipine, asphagen, dimeticone, falkamin, guaiazulene, hydrocortisone in eurax, hyoscine, ketoprofen, levothyroxine, lidocaine, olmesartan, paracetamol, prednisolone, sennoside a+b, tramadol, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, mass at left lower lobe of lung, and para-caval lymphadenopathy. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 26 Apr 2013 (Day 2), the subject experienced increased blood bilirubin (Grade 2) with total bilirubin 53.01 umol/L (NR: 3.42 – 18.81). On 15 May 2013 (Day 21), the event worsened to Grade 3 with total bilirubin 58.14 umol/L. On 16 May 2013 (Day 22), the study drug was interrupted. On 29 May 2013 (Day 35), the severity of increased blood bilirubin improved to Grade 2 with total bilirubin 51.3 umol/L. On 03 Jun 2013 (Day 40), the subject recovered from increased blood bilirubin. On 04 Jun 2013 (Day 41), the study drug was resumed at a reduced dose of 8 mg/day due to increased blood bilirubin. The Investigator considered increased blood bilirubin nonserious and probably related to the study drug.

On 16 Jun 2015 (Day 783), the subject experienced low back pain and was admitted to the hospital for further evaluation. The subject was diagnosed with spinal compression fracture (fractured compression at L1 due to aging; Grade 3) confirmed by spinal x-ray. The subject was treated with paracetamol, ketoprofen, and tramadol. On 19 Jun 2015 (Day 786), the subject experienced hepatic failure (Grade 3), decreased weight (Grade 3) with weight of 50.3 kg (Baseline: 65 kg), and decreased platelet count (Grade 2). Laboratory tests showed platelets 63 x10^9/L (NR: 158 – 348), albumin 21 g/L (NR: 35 – 55), ALP 108 U/L (NR: 43 – 115), ALT 56 U/L (NR: 10 – 40), AST 199 U/L (NR: 10 – 43), and total bilirubin 88.1 umol/L (NR: 0 – 18.8). The subject experienced decreased appetite (Grade 2) since 11 Feb 2015 (Day 658) and on 24 Jun 2015 (Day 791), the study drug was interrupted due to decreased appetite and hepatic failure. On 25 Jun 2015 (Day 792), the severity of decreased appetite worsened to Grade 3 and decreased platelet count improved to Grade 1. Repeat laboratory tests showed albumin 18 g/L (NR: 41 – 51) and platelets 81 x10^9/L. The subject was treated with amino acids w/electrolytes/glucose/thiamine. On 25 Jun 2015 (Day 792), the subject was withdrawn from the study due to hepatic failure and the subject received the last dose on

23 Jun 2015 (Day 790). The subject was recovering from spinal compression fracture and did not recover from hepatic failure and decreased platelet count. The outcome of decreased appetite and decreased weight was unknown. The Investigator considered spinal compression fracture, hepatic failure serious and not related to the study drug; decreased platelet count nonserious and possibly related to the study drug; decreased appetite and decreased weight nonserious and not related to the study drug.

On 21 Feb 2016 (Day 1033, 243 days after the last dose), the subject died due to clinical disease progression.

Subject Number	12201008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01509-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Pyrexia

A 67-year-old Japanese male was diagnosed with hepatocellular carcinoma on 08 Dec 2009. Significant medical history included cholecystectomy, duodenal ulcer, gastritis, gastric polyps, hepatitis C, hypertension, hepatic cirrhosis, and splenectomy. Previous anticancer therapies included hepatectomy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/vitamins, amlodipine, asphagen, cilnidipine, dimeticone, enzymes, esomeprazole, falkamin, furosemide, lidocaine, olmesartan, paracetamol, spironolactone, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed a lesion at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 21 May 2014 (Day 8), the subject was hospitalized for pyrexia (Grade 1) with temperature of 37.8℃. The subject was treated with paracetamol. Laboratory tests showed no increase in white blood cell or neutrophil counts. The study drug dose was not changed. The subject recovered from pyrexia on 28 May 2014 (Day 15). The Investigator considered pyrexia serious and possibly related to the study drug.

On 28 May 2014 (Day 15), the subject experienced hypoalbuminemia (Grade 2) with albumin 27 g/L (NR: 35 – 55). The study drug dose was not changed. On 09 Jul 2014 (Day 57), the subject experienced decreased appetite (Grade 1). The subject was treated with falkamin and amino acids w/vitamins. On 29 Jul 2014 (Day 77), the subject missed a dose of the study drug. On 30 Jul 2014 (Day 78), severity of hypoalbuminemia worsened to Grade 3 with albumin 19 g/L (NR: 38 – 50) and decreased appetite worsened to Grade 2. On the same day (Day 78), the study drug was interrupted due to decreased appetite. The subject was treated with falkamin. The subject did not recover from hypoalbuminemia and decreased appetite. The Investigator considered decreased appetite nonserious and probably related to the study drug; hypoalbuminemia nonserious and not related to the study drug.

On 28 Aug 2014 (Day 107), tumor response assessment showed disease progression. On 02 Sep 2014 (Day 112), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 28 Jul 2014 (Day 76).

On 12 Nov 2014 (Day 183, 107 days after the last dose), the subject died due to disease progression.

Subject Number	12201009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01537-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Ascites (3x), Duodenal ulcer haemorrhage
AE(s) Leading to Discontinuation	Ascites

A 70-year-old Japanese male was diagnosed with hepatocellular carcinoma on 13 Sep 2012. Significant medical history included contrast media allergy, duodenal ulcer, esophageal varices, gastritis, helicobacter pylori infection, hepatitis C, hypertension and liver cirrhosis. Previous anticancer therapies included high frequency ablation and transcatheter arterial chemoembolization. Prior and concomitant medications included alginic acid, amino acids w/vitamins, aminoleban, amlodipine, aprovasc, brotizolam, dimeticone, falkamin, furosemide, glucose, glycerol, human albumin, hyoscine, irbesartan, lactulose, lidocaine, paracetamol, prednisolone, rabeprazole, rebamipide, ringer-lactate, risperidone, sennoside a+b, silodosin, sodium chloride, solita-t1, spironolactone, teprenone, tolvaptan, urea, ursodeoxycholic acid, and vitamin U. 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 12 Jun 2014 (Day 1), treatment with study drug was initiated.

On 26 Jun 2014 (Day 15), the subject experienced proteinuria (Grade 3) with 24h urine protein 12.3004 g/24hr, decreased platelet count (Grade 2) with platelet count 64 x10^9/L (NR: 125 – 375), and hypertension (Grade 2). On 04 Jul 2014 (Day 23), the study drug was interrupted due to proteinuria. On 04 Jul 2014 (Day 23), the subject's hypertension worsened to Grade 3. On 08 Jul 2014 (Day 27), the subject was hospitalized for ascites (Grade 2) confirmed by abdominal ultrasound and the subject also had hypoalbuminemia (Grade 2), malaise (Grade 2), and leg edema (Grade 2). On the same day (Day 27), decreased platelet count improved to Grade 1. The study drug remained interrupted due to ascites. Laboratory test showed albumin 25 g/L (NR: 35 – 55), ALP 178 U/L (NR: 43 – 115), AST 56 U/L (NR: 10 – 43), and platelet count 94 x10^9/L. The subject was treated with amlodipine, aprovasc, furosemide, spironolactone, irbesartan, falkamin, and high protein diet therapy. On 15 Jul 2014 (Day 34), the subject recovered from proteinuria. On 16 Jul 2014 (Day 35), repeat abdominal ultrasound showed reduced volume of ascites. On 20 Jul 2014 (Day 39), the subject recovered from malaise. On 22 Jul 2014 (Day 41), the subject recovered from ascites and leg edema. On 23 Jul 2014 (Day 42), the subject recovered from decreased platelet count. On the same day (Day 42), the study drug was resumed at a reduced dose of 8 mg/day due to ascites. On 21 Sep 2014 (Day 102), the subject recovered from hypertension. The subject did not recover from hypoalbuminemia. The Investigator considered ascites serious and probably related to the study drug; proteinuria, hypertension, decreased platelet count, hypoalbuminemia, malaise, and leg edema nonserious and probably related to the study drug.

On 14 Sep 2014 (Day 95), the subject was hospitalized for duodenal ulcer hemorrhage (Grade 2). On 18 Sep 2014 (Day 99), the study drug was interrupted due to this event. On the same day (Day 99), the subject also experienced anemia (Grade 2), leg edema (Grade 2), hemorrhoidal hemorrhage (Grade 1), hypoalbuminemia (Grade 3), and hyponatremia (Grade 3) with sodium 128 mmol/L (NR: 138 – 146). Abdominal echocardiography showed moderate volume of ascites seen in liver surface, morrison's pouch, periphery of the spleen, and pelvic region. Colonoscopy showed black residues in all regions of large intestine and hemorrhoids. Laboratory tests showed albumin 19 g/L (NR: 38 – 50), Hgb 80 g/L (NR: 137 – 165), and BUN 17.4573 mmol/L (NR: 2.856 – 7.14). Upper gastrointestinal endoscopy showed duodenal ulcer A2 stage. The subject was transfused with packed red blood cells and treated with rebamipide, rabeprazole, alginic acid, and ringer-lactate. On 20 Sep 2014 (Day 101), the subject remained hospitalized for ascites (Grade 2) and the study drug remained interrupted due to duodenal ulcer hemorrhage and ascites. On 23 Sep 2014 (Day 104), the subject recovered from hemorrhoidal hemorrhage. On 24 Sep 2014 (Day 105), repeat abdominal ultrasound showed moderate volume of ascites retention and the subject underwent abdominal cavity drainage. Treatment included tolvaptan, furosemide, and human albumin. On 25 Sep 2014 (Day 106), the hypoalbuminemia improved to Grade 2 with albumin 20 g/L (NR: 38 – 50). On 26 Sep 2014 (Day 107), the subject experienced pleural effusion (Grade 1). The subject underwent thoracoabdominal angiogram which showed high volume of ascites between periphery of the liver and the pelvic region. On 29 Sep 2014 (Day 110), the hypoalbuminemia worsened to Grade 3 with albumin 19 g/L (NR: 38 – 50) and the subject was treated with human albumin. On 01 Oct 2014 (Day 112), the subject experienced delirium (Grade 1). On 02 Oct 2014 (Day 113), the ascites worsened to Grade 3. Laboratory tests showed albumin 25 g/L (NR: 35 – 55), ALT 49 U/L (NR: 10 – 40), AST 66 U/L (NR: 10 – 43), and BUN 8.92 mmol/L (NR: 1.78 – 7.14). On 02 Oct 2014 (Day 113), the subject was withdrawn from the study due to ascites and the subject received the last dose of the study drug on 17 Sep 2014 (Day 98). On 06 Oct 2014 (Day 117), a repeat abdominal ultrasound showed moderate volume of ascites in the liver surface, periphery of the spleen, and the pelvic region. On 07 Oct 2014 (Day 118), the leg edema worsened to Grade 3 and the subject experienced urinary retention (Grade 2). On 09 Oct 2014 (Day 120), the subject experienced hypernatremia (Grade 2) with sodium 150 mmol/L. On 10 Oct 2014 (Day 121), the subject experienced hepatic encephalopathy (Grade 2). On 12 Oct 2014 (Day 123), the subject recovered from hypernatremia with sodium 141 mmol/L. The subject was treated with lactulose, silodosin, and solita-t1. On 14 Oct 2014 (Day 125), the subject recovered from hepatic encephalopathy. On 15 Oct 2014 (Day 126), the anemia worsened to Grade 3 with Hgb 74 g/L. On 20 Oct 2014 (Day 131), the subject recovered from duodenal ulcer hemorrhage. On 25 Nov 2014 (Day 167), the subject's chest-abdominal CT scan showed decreased volume of ascites. On 26 Nov 2014 (Day 168), the subject recovered from ascites. The subject did not recover from anemia, leg edema, urinary retention, pleural effusion, delirium, and hypoalbuminemia. The Investigator considered duodenal ulcer hemorrhage serious and possibly related to study drug; ascites serious and probably related to study drug; hemorrhoidal hemorrhage, hyponatremia, pleural effusion nonserious and possibly related to the study drug; hypoalbuminemia, leg edema nonserious and probably related to study drug; anemia, delirium, hypernatremia, hepatic encephalopathy nonserious and not related to study drug.

On 25 Nov 2014 (Day 167), tumor response assessment showed disease progression.

On 20 May 2015 (Day 343, 245 days after the last dose), the subject died of unknown cause.

Subject Number	12211008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001539
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Lung abscess

A 67-year-old Japanese male was diagnosed with hepatocellular carcinoma on 08 Apr 2014. Significant medical history included chronic gastritis, chronic hepatitis B, hemorrhoids, hypertension, and large intestine polyp. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included ambroxol, benidipine, bromhexine, brotizolam, carbohydrates w/potassium chloride/sodium, ceftriaxone, clindamycin, clostridium butyricum, daikenchuto, dextromethorphan, dimeticone, entecavir, felbinac, flavine adenine dinucleotide, hyoscine, itopride, l-carbocysteine, levofloxacin, lidocaine, marzulene s, paracetamol, pronase, sodium picosulfate, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 08 Oct 2014 (Day 21), the subject experienced lung abscess (Grade 3). Treatment included paracetamol, carbohydrates w/potassium chloride/sodium, and flavine adenine dinucleotide. On 06 Nov 2014 (Day 50), the CT scan of chest showed lung abscess and the subject was hospitalized for further treatment on 07 Nov 2014 (Day 51). Treatment included bromhexine, carbohydrates w/potassium chloride/sodium, ceftriaxone, clindamycin, dextromethorphan, levofloxacin, ambroxol, and l-carbocysteine. On 12 Nov 2014 (Day 56), laboratory tests showed CRP 75.7 mg/L (NR: 0 – 5) and WBC 9.8 x10^9/L (NR: 3.7 – 11). On 28 Nov 2014 (Day 72), chest x-ray showed inflammatory findings and infiltrative shadows were improving. On 04 Dec 2014 (Day 78), the subject improved and was discharged from the hospital. On 10 Dec 2014 (Day 84), repeat laboratory tests showed WBC 6.9 x10^9/L and CRP 7.3 mg/L. On 07 Jan 2015 (Day 112), the subject recovered from lung abscess. The Investigator considered lung abscess serious and not related to study drug.

On 24 Dec 2014 (Day 98), the subject experienced decreased appetite (Grade 2). Treatment included itopride and marzulene s. On 21 Jan 2015 (Day 126), the body weight was 32.9 kg (Baseline: 41.7 kg). On 22 Jan 2015 (Day 127), the study drug dose was reduced to 4 mg/day due to decreased appetite. On 04 Mar 2015 (Day 168), the subject recovered from decreased appetite with body weight of 37.4 kg. The Investigator considered decreased appetite nonserious and possibly related to the study drug.

On 14 Aug 2015 (Day 331), tumor response assessment showed disease progression however, on 23 Apr 2015 (Day 218), the scans were initially assessed as partial response but later on 02 Oct 2015 (Day 380), the scans were reassessed as progressive disease. On 19 Aug 2015

(Day 336), the subject was withdrawn from the study due to disease progression and received the last dose on the same day (Day 336).

Subject Number	12241001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01311-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy
AE(s) Leading to Discontinuation	Hepatic encephalopathy

A 79-year-old Japanese male was diagnosed with hepatocellular carcinoma on 23 Apr 2013. Significant medical history included cancer pain, chronic hepatitis C, esophageal varices, hepatic cirrhosis, left upper pneumonectomy, and tuberculosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids w/electrolytes/glucose/thiamine, aminoleban, aminoleban en, amlodipine, betahistine, bromelains, carbohydrates w/potassium chloride/sodium, cefazolin, diclofenac, falkamin, glycerol, glycine max, heparinoid, intravenous vitamedin, kanamycin, lactulose, loperamide, loxoprofen, magnesium oxide, menatetrenone, mepivacaine, mexiletine, oxycodone, polaprezinc, prochlorperazine, sennoside a+b, solacet f, solita-t1, sulfadiazine, ultracet, urea, and zinc. At Screening, tumor assessments of target/non-target lesions via CT showed lesion at right lobe of liver; left shoulder girdle bone mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 18 Jul 2013 (Day 15), the subject was hospitalized for hepatic encephalopathy (Grade 4). The subject also experienced dehydration (Grade 4), constipation (Grade 1), cerebral infarction (Grade 1), and infection (unknown site; Grade 1). Laboratory tests showed ammonia 183.4723 umol/L (NR: 8.5668 – 47.1174), BUN 42.48 mmol/L (NR: 1.78 – 7.14), creatinine 186 umol/L (NR: 62 – 124), potassium 6 mmol/L (NR: 3.5 – 5), total bilirubin 49.2 umol/L (NR: 1.7 – 18.8), albumin 34 g/L (NR: 35 – 55), ALT 59 U/L (NR: 10 – 40), and AST 96 U/L (NR: 10 – 43). Treatment included aminoleban, aminoleban en, cefazolin, glycerol, kanamycin, lactulose, sennoside a+b, falkamin, magnesium oxide, diclofenac, carbohydrates w/potassium chloride/sodium, and amino acids with electrolytes/glucose. On 18 Jul 2013 (Day 15), the subject was withdrawn from the study due to hepatic encephalopathy and received last dose of study drug on 17 Jul 2013 (Day 14). On 20 Jul 2013 (Day 17), ammonia was 114.9379 umol/L. On 25 Jul 2013 (Day 22), the subject recovered from dehydration and infection. On 05 Aug 2013 (Day 33), the severity of hepatic encephalopathy improved to Grade 1 with ammonia 54.9703 umol/L and on 09 Sep 2013 (Day 68), the subject recovered from hepatic encephalopathy. The subject was recovering from cerebral infarction and constipation. The Investigator considered hepatic encephalopathy serious and not related to study drug; dehydration, infection, constipation, and cerebral infarction nonserious and not related to the study drug.

On 17 Dec 2013 (Day 167, 153 days after the last dose), the subject died due to unknown reason.

Subject Number	12251001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01471-CLI-JP
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Anaemia (2x)

A 77-year-old Japanese male was diagnosed with hepatocellular carcinoma on 31 May 2011. Significant medical history included abdominal pain, atrophic gastritis, chronic hepatitis C, constipation, diabetes mellitus, gastric ulcer, hypertension, and traumatic subarachnoid hemorrhage. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications, alginic acid, antibiotics-resistant lactic acid bacteria, asphagen, atropine, benzethonium, calcium gluconate, cefazolin, cefcapene, celecoxib, cilnidipine, clarithromycin, diclofenac, dimeticone, epinephrine, falkamin, flumazenil, furosemide, general nutrients, glucagon, human albumin, iron, irsogladine, levothyroxine, lidocaine, loxoprofen, magnesium citrate, magnesium oxide, menatetrenone, mepivacaine, midazolam, mosapride, nutrients, ora, oxidised cellulose, paracetamol, pentazocine, polaprezinc, pronase, rabeprazole, ringer-lactate, sitagliptin, sodium bicarbonate, sodium picosulfate, solacet f, spironolactone, timepidium, urea, ursodeoxycholic acid, and valisone-g. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of the liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 6.

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

On 28 Feb 2014 (Day 278), the subject experienced gastric ulcer (Grade 2) and the study drug was interrupted due to this event. Gastrointestinal endoscopy showed multiple ulcers from the lesser curvature of the gastric antrum to the pyloric ring, no ulcers in the duodenum. The subject was treated with rabeprazole, irsogladine, and polaprezinc. The subject did not recover from gastric ulcer. The Investigator considered gastric ulcer nonserious and possibly related to the study drug.

On 07 Mar 2014 (Day 285), the subject experienced anemia (Grade 2) with Hgb 100 g/L (NR: 136 – 170). On 24 Mar 2014 (Day 302), anemia worsened to Grade 3 with Hgb 72 g/L and the subject was hospitalized. The study drug remained interrupted due to anemia. On 28 Mar 2014 (Day 306), laboratory test showed Hgb 83 g/L (NR: 125 – 170). Repeat gastrointestinal endoscopy showed ulcer in the angular incisures and colonoscopy showed sporadic sigmoid diverticula. Treatment included intravenous iron (saccharated ferric oxide), human albumin, abdominal cavity drainage, and packed red blood cell transfusion. On 04 Apr 2014 (Day 313), anemia improved to Grade 1 with Hgb 104 g/L (NR: 136 – 170). The subject was recovering from anemia. The Investigator considered anemia serious and not related to study drug.

On 07 Apr 2014 (Day 316), the subject was found unconscious and underwent CPR and endotracheal intubation. The subject was treated with calcium gluconate and epinephrine. Whole body CT scan showed no traumatic head injury, no intraperitoneal bleeding or

gastrointestinal bleeding and no significant problems were noted in the great vessels. Later that day (Day 316, 39 days after the last dose), the subject died due to acute myocardial infarction. Autopsy showed broad necrosis in the cardiac muscle. The subject received the last dose of study drug on 27 Feb 2014 (Day 277). The Investigator considered acute myocardial infarction serious and not related to study drug.

Subject Number	12251007
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01556-CLI-JP
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Bile duct stone, Portal vein thrombosis, Hepatic encephalopathy

A 60-year-old Japanese male was diagnosed with hepatocellular carcinoma in Nov 2010. Significant medical history included chronic hepatitis B, chronic renal impairment, diabetes mellitus, esophageal varices, cholelithiasis, ruptured liver carcinoma, hepatic cirrhosis, and musculoskeletal (shoulder) pain. Previous anticancer therapies included radiotherapy to right lobe of liver, cisplatin, fluorouracil, hepatic intra-arterial chemotherapy, and transcatheter arterial chemoembolization. Prior and concomitant medications included ambroxol, aminoleban, amlodipine, antithrombin III, brotizolam, cefcapene, clobetasol, clostridium butyricum, codeine, danaparoid, diazepam, dimeticone, diphenhydramine, ecabet, entecavir, falkamin, flumazenil, furosemide, glucose 5% with ringer baxter, glyceryl trinitrate, gualenic acid, heparin, human albumin, human insulin, influenza vaccine, insulin aspart, isosorbide dinitrate, l-carbocysteine, lactulose, lidocaine, loxoprofen magnesium oxide, midazolam, nafamostat, olmesartan, paracetamol, pentazocine, pentoxyverine, pronase, rabeprazole, restamin cortizon, sennoside a+b, sodium bicarbonate, sodium chloride, spironolactone, tenofovir, timepidium, urea, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe, masses at left lingular lobe, right lower lobe, and multiple sites of lung. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 15 May 2014 (Day 24), the subject experienced decreased appetite (Grade 1). On 03 Jul 2014 (Day 73), decreased appetite worsened to Grade 2 and the study drug was interrupted. On 10 Jul 2014 (Day 80), the subject recovered from decreased appetite. The study drug was resumed at a reduced dose of 8 mg/day due to decreased appetite. The Investigator considered decreased appetite nonserious and probably related to the study drug.

On 06 Aug 2014 (Day 107), the subject experienced cholestatic jaundice (Grade 2). On 07 Aug 2014 (Day 108), the subject was hospitalized for bile duct stone (Grade 3). The subject underwent endoscopic retrograde cholangiopancreatography (ERCP) and the study drug was interrupted due to bile duct stone. Treatment included loxoprofen, ecabet, paracetamol, pentazocine, and nafamostat. On 11 Aug 2014 (Day 112), the subject experienced portal vein thrombosis (Grade 3) and underwent repeat ERCP followed by gallbladder lithotripsy. Repeat CT scan showed no common bile duct stones; thrombus formation in the region ranging from the portal vein to the right portal vein branch. Laboratory tests showed albumin 31 g/L (NR: 35 – 55), ALP 120 U/L (NR: 43 – 115), total bilirubin 50.4 umol/L (NR: 0 – 18.8), BUN 10.71 mmol/L (NR: 1.78 – 7.14), and creatinine 186 umol/L (NR: 62 – 124). The subject was treated with antithrombin III, danaparoid, and heparin. On 01 Sep 2014 (Day 133), the study drug was resumed at the same dose. On 05 Sep 2014 (Day 137), the subject recovered from

cholestatic jaundice and bile duct stone with total bilirubin 32.49 umol/L (NR: 5.13 – 20.52). On 08 Sep 2014 (Day 140), repeat CT scan showed slight reduction in portal vein thrombosis. The subject was recovering from portal vein thrombosis. The Investigator considered bile duct stone and portal vein thrombosis serious and not related to the study drug; cholestatic jaundice nonserious and not related to the study drug.

On 12 Sep 2014 (Day 144), the subject experienced intracranial hemorrhage (Grade 1) and CT scan of brain showed subcutaneous hemorrhage in the left occipital lobe. The subject was asymptomatic and no medical intervention was needed. Heparin was stopped but the study drug dose did not change. The subject did not recover from this event. The Investigator considered intracranial hemorrhage nonserious and possibly related to the study drug.

On 28 Nov 2014 (Day 221), the subject experienced increase blood bilirubin (Grade 3) with total bilirubin 85.5 umol/L (NR: 5.13 – 20.52). The study drug was interrupted due to the event. On 19 Dec 2014 (Day 242), the subject was hospitalized for hepatic encephalopathy (Grade 3) with ammonia 154 umol/L (NR: 11 – 32), total bilirubin 39.33 umol/L (NR: 5.13 – 20.52), and albumin 36 g/L (NR: 40 – 50). The study drug remained interrupted due to hepatic encephalopathy. The brain CT scan showed petechiae on cortex of right frontal lobe. Treatment included lactulose enema and aminoleban. On 26 Dec 2014 (Day 249), the subject recovered from increase blood bilirubin and repeat laboratory tests showed albumin 28 g/L (NR: 40 – 50), ammonia 43 umol/L, and total bilirubin 20.52 umol/L (NR: 5.13 – 20.52). On 27 Dec 2014 (Day 250), the subject recovered from hepatic encephalopathy. On 13 Jan 2015 (Day 267), the study drug was resumed at a reduced dose of 4 mg/day due to increase blood bilirubin. The Investigator considered hepatic encephalopathy serious and not related to the study drug; increase blood bilirubin nonserious and possibly related to the study drug.

On 26 Jan 2015 (Day 280), tumor response assessment showed disease progression and the subject was withdrawn from study due to disease progression. The subject received the last dose of the study drug on the same day (Day 280).

On 27 Apr 2015 (Day 371, 91 days after the last dose), the subject died due to disease progression.

Subject Number	12251010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000762
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Muscular weakness, Hepatic encephalopathy (3x)
AE(s) Leading to Discontinuation	Hepatic encephalopathy

An 84-year-old Japanese female was diagnosed with hepatocellular carcinoma in Jun 2007. Significant medical history included iron deficiency anemia, chronic gastritis, chronic hepatitis C, esophageal varices, hyperammonemia, hypertension, hypothyroidism, ileus, hepatic cirrhosis, periodic paralysis, uterine cancer, and vertigo. Previous anticancer therapies included hepatectomy, high frequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included aczym, adenosine, aminoleban, amlodipine, asphagen, bisacodyl, ceftriaxone, diazepam, diltiazem, dimeticone, falkamin, glucose, gualenic acid, iron, lactulose, levocarnitine, levofloxacin, levothyroxine, lidocaine, loxoprofen, magnesium oxide, metoclopramide, olmesartan, polaprezinc, prochlorperazine, pronase, rabeprazole, sodium bicarbonate, timepidium, urea, ursodeoxycholic acid, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and caudate lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 16 Sep 2014 (Day 5), the subject experienced hyperammonemia (Grade 1) with ammonia 160 umol/L (NR: 11 – 32) and malaise (Grade 1). The subject was treated with lactulose and levocarnitine. On 18 Sep 2014 (Day 7), severity of malaise worsened to Grade 2. On the same day (Day 7), the study drug was interrupted due to malaise. On 22 Sep 2014 (Day 11), severity of malaise improved to Grade 1 and the study drug was resumed at a reduced dose of 4 mg/day due to malaise. The subject did not recover from malaise and hyperammonemia. The Investigator considered malaise nonserious and probably related to the study drug; hyperammonemia nonserious and possibly related to the study drug.

On 06 Oct 2014 (Day 25), the subject experienced muscular weakness in limbs (Grade 2) associated with dizziness on standing and loss of balance. On 07 Oct 2014 (Day 26), the subject was hospitalized and the study drug was interrupted. The electrocardiogram was abnormal but not clinically significant. The cause of muscular weakness was unknown and no treatment was given. On 15 Oct 2014 (Day 34), severity of muscular weakness improved to Grade 1. On 21 Oct 2014 (Day 40), the subject recovered from muscular weakness and the study drug was resumed at a reduced frequency of 4 mg every other day due to this event. The Investigator considered muscular weakness serious and possibly related to the study drug.

On 14 Dec 2014 (Day 94), the subject was having strange behavior and unresponsiveness and was hospitalized with a diagnosis of hepatic encephalopathy (Grade 3). The subject also experienced dehydration (Grade 1). The study drug was interrupted due to hepatic

encephalopathy. Laboratory tests showed AST 93 U/L (NR: 13 – 33), ALP 339 U/L (NR: 115 – 359), and ammonia 122 umol/L. The computerized tomography scan of the head showed no abnormalities. The subject was treated with aminoleban, gualenic acid, and asphagen. On 18 Dec 2014 (Day 98), the study drug was resumed at the same dose. On 23 Dec 2014 (Day 103), the subject recovered from hepatic encephalopathy and dehydration. The Investigator considered hepatic encephalopathy serious and possibly related to the study drug; dehydration nonserious and not related to the study drug.

On 21 Jan 2015 (Day 132), the subject was hospitalized for hepatic encephalopathy (Grade 3) with symptom of unresponsiveness. The subject also experienced urinary retention (Grade 3) and dehydration (Grade 1). The study drug was interrupted due to hepatic encephalopathy. The CT scan of head showed no abnormalities. The subject underwent bladder catheterization and was treated with aminoleban and glucose. On the same day (Day 132), the subject recovered from urinary retention. On 22 Jan 2015 (Day 133), laboratory tests showed AST 89 U/L (NR: 13 – 33), ALT 60 U/L (NR: 8 – 42), and ammonia 96 umol/L. On 27 Jan 2015 (Day 138), repeat laboratory tests showed albumin 29 g/L (NR: 35 – 55), ALT 40 U/L (NR: 10 – 33), AST 61 U/L (NR: 10 – 36), creatinine 44 umol/L (NR: 62 – 124), ammonia 76 umol/L, and potassium 4.6 mmol/L (NR: 3.5 – 5). On the same day (Day 138), the study drug was resumed at the same dose. On 28 Jan 2015 (Day 139), the subject recovered from hepatic encephalopathy and dehydration. The Investigator considered hepatic encephalopathy serious and possibly related to the study drug; urinary retention and dehydration nonserious and not related to the study drug.

On 14 Feb 2015 (Day 156), the subject was hospitalized for hepatic encephalopathy (Grade 3) and the study drug was interrupted. A CT scan of head showed no abnormalities. The subject was treated with aminoleban and glucose. Laboratory tests showed AST 72 U/L (NR: 13 – 33), ALT 50 U/L (NR: 8 – 42), and ammonia 198 umol/L. On 19 Feb 2015 (Day 161), the subject was withdrawn from the study due to hepatic encephalopathy and received the last dose of the study drug on 13 Feb 2015 (Day 155). On 20 Feb 2015 (Day 162), the subject recovered from hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and possibly related to the study drug.

On 16 Jan 2016 (Day 492, 337 days after the last dose), the subject died due to unknown reason.

Subject Number	14021008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-013904
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Gastrointestinal viral infection

A 71-year-old white male was diagnosed with hepatocellular carcinoma on 30 Nov 2012. Significant medical history included anxiety, atopic dermatitis, colic abdominal pain, large intestinal polypectomy, depression, diabetes mellitus, ex-alcoholic, gastric ulcer, hypercholesterolemia, hypertension, pain in jaw, petechiae, prostate cancer, purpura, sleep disorder, and urinary incontinence. Previous anticancer therapies included radiotherapy to hepatic lymph node, transcatheter arterial chemoembolization (2x), and hepatectomy. Prior and concomitant medications included acetylsalicylic acid, atenolol, betamethasone, carbohydrates w/fats/minerals, citalopram, cortivazol, diclofenac, fosfomycin, ketoprofen, lorazepam, macrogol, nicardipine, paracetamol, pregabalin, rosuvastatin, sitagliptin, solifenacin, spasfon, and zopiclone. At Screening, tumor assessment of target/non target lesion via CT scan showed lesions at left lobe of liver and hepatic dome. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 11 Jan 2016 (Day 405), the subject experienced diarrhea (Grade 2) and treatment was not provided. On 18 Jan 2016 (Day 412), the subject experienced abdominal pain (Grade 2) and vomiting (Grade 1) and was hospitalized with a diagnosis of gastrointestinal viral infection (Grade 2). The subject was treated with paracetamol. On 25 Jan 2016 (Day 419), the subject recovered from abdominal pain and vomiting. On 26 Jan 2016 (Day 420), the study drug was interrupted due to gastrointestinal viral infection. On the same day (Day 420), the subject recovered from diarrhea. On 28 Jan 2016 (Day 422), the laboratory tests showed sodium 132 mmol/L (NR: 133 – 145) and creatinine 71 umol/L (NR: 62 – 124). On 01 Feb 2016 (Day 426), the subject recovered from gastrointestinal viral infection and the study drug was resumed at the same dose. The Investigator considered gastrointestinal viral infection serious and not related to the study drug; diarrhea, abdominal pain, and vomiting nonserious and not related to the study drug.

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

Subject Number	14021014
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-012671
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Myocardial infarction
AE(s) Leading to Discontinuation	Myocardial infarction

A 57-year-old white male was diagnosed with hepatocellular carcinoma on 27 Dec 2014. Significant medical history included alcohol abuse, peritoneal hemorrhage, hypertension, hepatic cirrhosis, hepatic hemorrhage, and tobacco poisoning. Previous anticancer therapies included transcatheter arterial chemoembolization (2x). Prior and concomitant medications included acetylsalicylic acid, amlodipine, atorvastatin, betamethasone, bisoprolol, coveram, esomeprazole, fondaparinux, ketoprofen, paracetamol, ticagrelor, tramadol, and unspecified herbal and traditional medicine (balsamic dye). At Screening, tumor assessments of target/non-target lesions via CT showed lesions at right liver lobe and liver tumoral infiltration; and lumbar vertebral mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 28 Apr 2015 (Day 1), treatment with study drug was initiated.

On 14 Jul 2015 (Day 78), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2) and was treated with betamethasone. On 21 Jul 2015 (Day 85), the study drug dose was reduced to 8 mg/day due to this event. On 18 Aug 2015 (Day 113), the subject recovered from this event. The Investigator considered this event nonserious and possibly related to the study drug.

On 06 Dec 2015 (Day 223), the subject experienced retrosternal burning pain without radiation and was hospitalized for myocardial infarction (Grade 3). On 08 Dec 2015 (Day 225), laboratory tests showed increased blood creatinine phosphokinase, increased blood creatinine phosphokinase MB, and increased troponin. Electrocardiogram showed myocardial infarction and coronary arteriogram showed “hurts monotronculars”. The subject underwent stent placement and was treated with acetylsalicylic acid, atorvastatin, fondaparinux, and ticagrelor. On the same day (Day 225), the subject recovered from this event and was withdrawn from the study due to myocardial infarction. The subject received the last dose of the study drug on 07 Dec 2015 (Day 224). The Investigator considered myocardial infarction serious and possibly related to the study drug.

On 03 Oct 2016 (Day 525, 301 days after the last dose), the subject died due to disease progression.

Subject Number	14061017
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-009598
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Abdominal pain (2x), Asthenia

A 50-year old African American male was diagnosed with hepatocellular carcinoma in Nov 2014. Significant medical history included hepatitis B and hypertension. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included enoxaparin, entecavir, esomeprazole, furosemide, metoclopramide, morphine, movicol, oxycodone, panadeine co, pantoprazole, prednisone, proteins (fortimel), spasfon, spironolactone, and valsartan. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right lobe, quadrate lobe, and portal vein of liver, and lung mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 09 Jun 2015 (Day 54), the subject experienced abdominal pain (Grade 2), asthenia (Grade 3), upper abdominal pain (epigastric pain; Grade 2), and was treated with oxycodone and pantoprazole. On 15 Jun 2015 (Day 60), asthenia improved to Grade 1. On 15 Jun 2015 (Day 60), tumor response assessment showed disease progression. On 16 Jun 2015 (Day 61), the study drug was reduced to 8 mg/day due to these events. On 13 Jul 2015 (Day 88), abdominal pain worsened to Grade 3. On the same day (Day 88), the subject was withdrawn from the study due to disease progression and received the last dose on 13 Jul 2015 (Day 88). The subject did not recover from upper abdominal pain, asthenia, and abdominal pain. The Investigator considered asthenia nonserious and probably related to study drug; abdominal pain, upper abdominal pain nonserious and not related to study drug.

On 29 Jul 2015 (Day 104), the subject was hospitalized for abdominal pain (Grade 2). Treatment included morphine, prednisone, and oxycodone. The subject did not recover from this event. On 04 Aug 2015 (Day 110), the subject was discharged from the hospital. On 07 Aug 2015 (Day 113), the subject was re-hospitalized for abdominal pain (Grade 2), asthenia (Grade 2), and also experienced nausea (Grade 1). The subject was treated with spasfon, esomeprazole, and morphine; prednisone, oxycodone were continued. On 20 Aug 2015 (Day 126), abdominal pain improved to Grade 1 but the subject remained hospitalized due to persistence of abdominal pain with stable asthenia. On 27 Aug 2015 (Day 133), the subject recovered from asthenia, abdominal pain, and nausea, and was discharged from the hospital. The Investigator considered abdominal pain and asthenia serious and not related to study drug; nausea nonserious and not related to study drug.