Subject Number	30091027
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-013711
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Diarrhoea

A 66-year-old Asian male was diagnosed with hepatocellular carcinoma on 08 Jan 2009. Significant medical history included large intestinal polypectomy, hepatitis B, hyperlipidemia, hypertension, cholecystectomy, contrast media allergy, and tuberculosis. Previous anticancer therapies included hepatectomy and transcatheter arterial chemoembolization. Prior and concomitant medications included atorvastatin, bisoprolol, blopress plus, bromhexine, candesartan, cefpodoxime, chlorphenamine, cimetidine, cough and cold preparations, diosmectite, efonidipine, erdosteine, esomeprazole, famotidine, fish oil, furosemide, glucose, hydrochlorothiazide, ibuprofen, loperamide, medilac-s, megestrol, metoclopramide, nicergoline, nifedipine, potassium chloride/sodium chloride, rosuvastatin, sodium bicarbonate, sodium chloride, spironolactone, tiropramide, trimebutine, twynsta, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at caudate liver lobe, hepatoduodenal ligament lymphadenopathy, and multiple bilateral lung lesions. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 08 Aug 2014 (Day 1), treatment with study drug was initiated.

On 03 Jan 2015 (Day 149), the subject experienced diarrhea (Grade 1). On 27 Mar 2015 (Day 232), the event worsened to Grade 3. The subject was treated with loperamide. On 04 Apr 2015 (Day 240), the study drug was interrupted due to diarrhea. On 05 Apr 2015 (Day 241), the subject recovered from diarrhea. On 08 Apr 2015 (Day 244), the study drug was resumed at a reduced dose of 8 mg/day due to this event. The Investigator considered diarrhea nonserious and possibly related to the study drug.

On 14 Jan 2016 (Day 525), the subject experienced diarrhea (drug induced diarrhea; Grade 2) and vomiting (Grade 2). On the same day (Day 525), the study drug was interrupted due to diarrhea. On 15 Jan 2016 (Day 526), the subject was hospitalized for diarrhea (Grade 3). The subject was treated with metoclopramide, sodium chloride, glucose, loperamide, and potassium chloride/sodium chloride. On 16 Jan 2016 (Day 527), the subject recovered from diarrhea. On 17 Jan 2016 (Day 528), the subject recovered from vomiting. On 21 Jan 2016 (Day 532), the study drug was resumed at a reduced dose of 4 mg/day due to diarrhea. The Investigator considered diarrhea serious and possibly related to the study drug; vomiting nonserious and possibly related to the study drug.

On 17 Feb 2016 (Day 559), tumor response assessment showed disease progression. On 19 Feb 2016 (Day 561), 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 561).

Subject Number	30101003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01492-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Headache, Vomiting
AE(s) Leading to Discontinuation	Headache

A 48-year-old Asian male was diagnosed with hepatocellular carcinoma on 16 Jun 2011. Significant medical history included increased alpha 1 fetoprotein, decreased appetite, chronic hepatitis B, hepatic cirrhosis, and abdominal pain upper (right subcostal pain). Previous anticancer therapies included transcatheter arterial chemoembolization, and radiotherapy to mass in left lobe of liver. Prior and concomitant medications included amino acids w/calcium chloride, amlodipine, digestives including enzymes (magenal-f), entecavir, fluorometholone, glutathione, hyaluronic acid, itopride, megestrol, metoclopramide, morphine, multiblue5, nicardipine, oxycodone, pethidine, prednisolone, sodium chloride, targin, tetracosactide, tramadol, ultracet, and zinc. At Screening, tumor assessments of target/non-target lesions via CT scan showed gastric lymphadenopathy, lesions at quadrate lobe and right lobe of liver, left and middle hepatic vein tumor thrombosis and quadrate portal vein branch tumor thrombosis, and mass in bilateral lower lobes of lung. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 11 Apr 2014 (Day 1), treatment with study drug was initiated.

On 30 Apr 2014 (Day 20), the subject experienced left sided headache (Grade 3). On 01 May 2014 (Day 21), the subject experienced vomiting (Grade 3). On 02 May 2014 (Day 22), the subject was hospitalized for headache and vomiting. The MRI showed newly visible enhancing mass at left cavernous sinus. The study drug was interrupted due to these events on the following day (Day 23). Treatment included amino acids w/calcium chloride, tramadol, pethidine, ultracet, targin, morphine, oxycodone, prednisolone, sodium chloride, glutathione, zinc, multiblue5, and metoclopramide. On 04 May 2014 (Day 24), the subject experienced left 3rd cranial nerve palsy (Grade 3). On 05 May 2014 (Day 25), the subject experienced hypertension (Grade 2) with BP of 145/84 mmHg. Treatment included hyaluronic acid, fluorometholone, nicardipine, and amlodipine. On 07 May 2014 (Day 27), the tumor response assessment showed disease progression with metastases in brain. On 08 May 2014 (Day 28), the study drug was withdrawn due to headache secondary to disease progression and the subject received the last dose of study drug on 02 May 2014 (Day 22). The subject was discharged from the hospital on 12 May 2014 (Day 32). The subject recovered from vomiting on 16 May 2014 (Day 36). The subject did not recover from headache, hypertension, and left 3rd cranial nerve palsy. On 19 May 2014 (Day 39), the subject underwent gamma radiation therapy to brain. The Investigator considered vomiting and headache serious and not related to study drug but related to disease progression; hypertension and left 3rd cranial nerve palsy nonserious and not related to study drug.

On 21 Jun 2014 (Day 72, 50 days after the last dose), the subject died due to disease progression. Autopsy was not performed.

Subject Number	30111003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01491-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy

A 59-year-old Asian male was diagnosed with hepatocellular carcinoma on 30 Dec 2012. Significant medical history included diabetes mellitus, esophagitis, hepatitis B, ruptured hepatoma, hypertension, hepatic cirrhosis, chronic gastritis, gastroesophageal reflux disease, and portal hypertensive gastropathy. Previous anticancer therapies included transarterial chemoembolization and radiotherapy to sternal mass. Prior and concomitant medications included eucreas (metformin/vidagliptin), falkamin, fentanyl, human insulin, hydroxyzine, ilaprazole, lactitol, lactulose, levosulpiride, magnesium oxide, megestrol, metoclopramide, oxycodone, pantoprazole, propranolol, smofkabiven perifer, targin, tenofovir, tramadol, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left lobe of liver and sternal mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 08 Apr 2014 (Day 23), the subject experienced noncardiac chest pain (Grade 1). The subject was treated with oxycodone and ultracet. The study drug dose was not changed. On 27 Apr 2014 (Day 42), the subject was hospitalized for hepatic encephalopathy (Grade 3) and the severity of noncardiac chest pain increased to Grade 2. Treatment included oxycodone, ultracet, tramadol, targin, fentanyl, lactitol, smofkabiven perifer, lactulose, and hydroxyzine. Laboratory tests showed ammonia 218 umol/L (NR: 0 – 40). The study drug was interrupted due to noncardiac chest pain and hepatic encephalopathy. On 29 Apr 2014 (Day 44), the subject recovered from hepatic encephalopathy. Laboratory tests showed ammonia 45 umol/L, total bilirubin 27.9 umol/L (NR: 1.7 – 18.8), and albumin 32 g/L (NR: 35 – 55). On 03 May 2014 (Day 48), the subject recovered from noncardiac chest pain and was discharged from the hospital. On 09 May 2014 (Day 54), the study drug was resumed at reduced dose of 4 mg/day due to these events. The Investigator considered hepatic encephalopathy serious and not related to study drug; noncardiac chest pain nonserious and not related to study drug.

On 04 Jul 2014 (Day 110), the tumor response assessment showed disease progression. On 08 Jul 2014 (Day 114), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 07 Jul 2014 (Day 113).

On 10 Sep 2014 (Day 178, 65 days after the last dose), the subject died due to disease progression.

Subject Number	30111006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-002440
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy

A 65-year-old Asian male was diagnosed with hepatocellular carcinoma on 08 Oct 2013. Significant medical history included abdominal pain, appendicectomy, duodenitis, epistaxis, gastroesophageal reflux disease, hepatitis B, hypertension, reflux laryngitis, hepatic cirrhosis, and portal hypertensive gastropathy. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylcysteine, amlodipine, ceftriaxone, cimetropium, ciprofloxacin, dexlansoprazole, fentanyl, furosemide, ilaprazole, lactulose, levosulpiride, magnesium oxide, metoclopramide, metronidazole, mosapride, oxycodone, pantoprazole, pennel, pethidine, piperacillin sodium w/tazobactam, potassium, propacetamol, saccharomyces boulardii, silybum marianum, spironolactone, targin, tenofovir, tramadol, ultracet, ursodeoxycholic acid, valsartan, and vitamins with minerals. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 11 Sep 2014 (Day 29), the subject experienced decreased platelet count (Grade 2). On 08 Oct 2014 (Day 56), the decreased platelet count worsened to Grade 3 with platelet count 52 x10^9/L (NR: 125 – 375) and the subject also experienced increased blood bilirubin (Grade 2) with total bilirubin 38.5 umol/L (NR: 1.7 – 18.8). On the same day (Day 56), the study drug was interrupted due to these events. On 15 Oct 2014 (Day 63), the subject recovered from decreased platelet count with platelet count 86 x10^9/L. On 12 Nov 2014 (Day 91), the subject recovered from increased blood bilirubin with total bilirubin 23.9 umol/L. On the same day (Day 91), the study drug was resumed at a reduced dose of 8 mg/day due to increased blood bilirubin. The Investigator considered decreased platelet count and increased blood bilirubin nonserious and possibly related to the study drug.

On 26 Nov 2014 (Day 105), the subject experienced decreased weight (Grade 2) with body weight 60.7 kg (Screening: 70.2 kg), increased blood bilirubin (Grade 3) with total bilirubin 58.14 umol/L (NR: 3.42 – 17.1), and decreased platelet count (Grade 3) with platelet count 45 x10^9/L (NR: 140 – 440). The study drug was interrupted on the same day (Day 105) due to these events. On 04 Dec 2014 (Day 113), the subject recovered from decreased platelet count with platelet count 64 x10^9/L (NR: 125 – 375). The subject did not recover from decreased weight and increased blood bilirubin. The Investigator considered decreased weight, decreased platelet count, and increased blood bilirubin nonserious and possibly related to the study drug.

On 02 Dec 2014 (Day 111), tumor response assessment showed disease progression. On 04 Dec 2014 (Day 113), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on 25 Nov 2014 (Day 104).

On 09 Dec 2014 (Day 118), the subject experienced hepatic encephalopathy (Grade 3). Laboratory tests showed ammonia 141 umol/L (NR: 0 – 40), AST 115 U/L (NR: 10 – 33), ALT 110 U/L (NR: 4 – 50), and total bilirubin 61.56 umol/L (NR: 3.42 – 17.1). On 10 Dec 2014 (Day 119), the subject was hospitalized for hepatic encephalopathy. The subject was treated with lactulose enema, acetylcysteine, ceftriaxone, lactulose, potassium, metronidazole, piperacillin sodium w/tazobactam, and ciprofloxacin. On 17 Dec 2014 (Day 126), the subject was treated with repeat lactulose enema. On 26 Dec 2014 (Day 135), ammonia was 49 umol/L. On 27 Dec 2014 (Day 136), the subject recovered from hepatic encephalopathy. The Investigator considered hepatic encephalopathy serious and not related to the study drug.

Subject Number	30121003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01412-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Abdominal pain

A 53-year-old Asian male was diagnosed with hepatocellular carcinoma on 16 Jul 2013. Significant medical history included erosive gastritis, hepatitis B, and hypertension. Previous anticancer therapies included radiotherapy to the right liver lobe and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, cefotaxime, cefpodoxime, desonide, fentanyl, lactulose, metronidazole, minerals w/vitamins, oxycodone, pantoprazole, paracetamol, pennel, propacetamol, propofol, silybum marianum, tramadol, and ultracet. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right and left lobes of the liver and thrombus in the mid hepatic vein; CT scan showed masses at bilateral lobes of the lung. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 02 Dec 2013 (Day –3), the subject experienced increased aspartate aminotransferase (Grade 3) and abdominal pain (Grade 1). Laboratory tests showed AST 408 U/L (NR: 10 – 43) and ALT 105 U/L (NR: 10 – 40). The subject was treated with ultracet. The subject was recovering from increased aspartate aminotransferase and did not recover from abdominal pain. The Investigator considered abdominal pain and increased aspartate aminotransferase nonserious and not related to the study drug.

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

On 10 Dec 2013 (Day 6), the subject was hospitalized for worsening of abdominal pain (Grade 2). The subject also experienced hyponatremia (Grade 3) and increased lipase (Grade 3). Laboratory tests showed albumin 31 g/L (NR: 35 – 55), ALP 46 U/L (NR: 43 – 115), ALT 116 U/L, AST 428 U/L, lipase 150 U/L (NR: 13 – 60), and sodium 127 mmol/L (NR: 133 – 145). On the same day (Day 6), the study drug was interrupted due to increased aspartate aminotransferase. On 11 Dec 2013 (Day 7), the subject experienced pyrexia (Grade 1). On 14 Dec 2013 (Day 10), the subject experienced ascites (Grade 1). The subject was treated with ultracet, tramadol, oxycodone, cefpodoxime, propacetamol, fentanyl, and paracetamol. On 16 Dec 2013 (Day 12), the subject recovered from pyrexia. On 19 Dec 2013 (Day 15), the subject experienced decreased lymphocyte count (Grade 3) with absolute lymphocytes 0.4 x10^9/L (NR: 0.9 – 3.6). On the same day (Day 15), the subject recovered from hyponatremia and increased lipase; the severity of abdominal pain improved to Grade 1 and increased aspartate aminotransferase improved to Grade 2 with AST 150 U/L. On 26 Dec 2013 (Day 22), severity of increased aspartate aminotransferase worsened to Grade 3 with AST 240 U/L. On 02 Jan 2014 (Day 29), the subject recovered from decreased lymphocyte count. The subject did not recover from abdominal pain, increased aspartate aminotransferase, and ascites. The Investigator considered abdominal pain serious and not related to the study drug; hyponatremia, increased aspartate aminotransferase, pyrexia, decreased lymphocyte count,

and ascites nonserious and not related to the study drug; increased lipase nonserious and possibly related to the study drug.

On 13 Jan 2014 (Day 40), the subject was withdrawn from the study by subject's choice and the last dose of the study drug was received on 09 Dec 2013 (Day 5).

On 20 Jan 2014 (Day 47), tumor response assessment showed disease progression.

On 30 Jan 2014 (Day 57, 52 days after the last dose), the subject died due to disease progression.

Subject Number	30121005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01473-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Pulmonary tuberculosis

A 65-year-old Asian male was diagnosed with hepatocellular carcinoma on 16 Dec 2008. Significant medical history included diabetes mellitus, gastric cancer, hepatitis C, hypertension, hepatic cirrhosis, groin pain, renal cyst, and nephrolithiasis. Previous anticancer therapies included hepatectomy, high frequency ablation, and diaphragmatic operation (wedge resection of diaphragm). Prior and concomitant medications included aceclofenac, acetylcysteine, alanyl glutamine, almagate, amlodipine, atropine, benzydamine, diprogenta, ecabet, eperisone, ethambutol, fentanyl, glimepiride, human insulin, isoniazid, lactulose, lidocaine, losartan, megestrol, metoclopramide, minerals w/vitamins, morphine, myprodol, oxycodone, pantoprazole, pennel, pethidine, pyrazinamide, pyridoxine, rifampicin, silybum marianum, targin, teprenone, tramadol, and triamcinolone. At Screening, tumor assessments of target/non-target lesions via CT scan showed bilateral lung masses and left upper cervical lymphadenopathy; MRI showed right pleural mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5

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

On 24 Mar 2014 (Day 110), tumor response assessment showed disease progression. On 31 Mar 2014 (Day 117), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 30 Mar 2014 (Day 116).

On 31 Mar 2014 (Day 117), the subject had a computerized tomography of chest which showed probably active pulmonary tuberculosis and a slightly increased amount of lower paraesophageal fluid collection. The subject was subsequently hospitalized for pulmonary tuberculosis (Grade 2). On 02 Apr 2014 (Day 119), bronchoscopy confirmed diagnosis of pulmonary tuberculosis and bronchial washing showed positive for acid fast bacilli. The subject was treated with ethambutol, isoniazid, pyrazinamide, pyridoxine, and rifampicin. The subject did not recover from pulmonary tuberculosis. The Investigator considered pulmonary tuberculosis serious and not related to the study drug.

Subject Number	30121016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01495-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Abdominal pain upper
AE(s) Leading to Discontinuation	Abdominal pain upper

A 66-year-old Asian male was diagnosed with hepatocellular carcinoma on 30 Oct 2013. Significant medical history included benign prostatic hyperplasia, esophageal varices, gastritis, hepatitis B, hypertension, left ventricular hypertrophy, splenomegaly, and ascites. Previous anticancer therapy included hepatectomy (2x). Prior and concomitant medications included amlodipine, bethanechol, cefotaxime, cefpodoxime, doxazosin, entecavir, falkamin, lactulose, metoclopramide, metronidazole, minerals w/vitamins, pantoprazole, paracetamol, pennel, propacetamol, propofol, silybum marianum, smofkabiven perifer, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lung mass at left upper and lingular lobes of lung, and lymphadenopathy at mediastinum; MRI showed lesions at right and left lobes of liver. The BCLC stage was C, ECOG performance score was 0, and Child Pugh score was 6.

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

On 03 May 2014 (Day 2), the subject was hospitalized for upper abdominal pain (epigastric pain; Grade 2) and also experienced decreased appetite (Grade 2). The subject was treated with tramadol, metoclopramide, propacetamol, lactulose, pantoprazole, and smofkabiven perifer. From 05 May 2014 (Day 4) until 13 May 2014 (Day 12), the subject missed all doses of the study drug. On 06 May 2014 (Day 5), subject experienced pyrexia (Grade 1) and was treated with cefotaxime and cefpodoxime. On 08 May 2014 (Day 7), the subject recovered from pyrexia and the severity of upper abdominal pain improved to Grade 1. On 13 May 2014 (Day 12), the subject was withdrawn from the study due to upper abdominal pain and by subject's choice. The subject received the last dose of the study drug on 04 May 2014 (Day 3). On 10 Jun 2014 (Day 40), the subject recovered from upper abdominal pain. The subject did not recover from decreased appetite. The Investigator considered upper abdominal pain serious and not related to the study drug; decreased appetite nonserious and possibly related to the study drug; pyrexia nonserious and not related to the study drug.

On 17 Jun 2014 (Day 47, 44 days after the last dose), the subject died due to disease progression.

Subject Number	30121018
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01544-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Decreased appetite, Flank pain

A 62-year-old Asian male was diagnosed with hepatocellular carcinoma on 08 May 2013. Significant medical history included emphysema, hypertension, hepatic cirrhosis, and splenomegaly. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included amlodipine, benzydamine, cefotaxime, cefpodoxime, falkamin, fentanyl, losartan, megestrol, pennel, propofol, silybum marianum, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed left mediastinal lymphadenopathy; MRI showed lesions at left and right liver lobes and para-aortic lymphadenopathy. The BCLC Stage was C, ECOG performance was 0, and Child Pugh score was 5.

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

On 01 Jul 2014 (Day 6), the subject experienced decreased appetite (Grade 1) and was treated with megestrol. On 22 Jul 2014 (Day 27), severity of decreased appetite worsened to Grade 3 and the subject was hospitalized. The subject's body weight decreased to 42 kg (Baseline: 44 kg). On 23 Jul 2014 (Day 28), the study drug was interrupted due to the event. On 28 Jul 2014 (Day 33), decreased appetite improved to Grade 1 and the subject was discharged from the hospital. On 28 Jul 2014 (Day 33), the study drug was resumed at reduced dose of 4 mg/day due to decreased appetite. On 05 Aug 2014 (Day 41), the subject recovered from decreased appetite. The Investigator considered decreased appetite serious and possibly related to study drug.

On 18 Aug 2014 (Day 54), the subject was hospitalized for right flank pain (Grade 2) which was persistent since 05 Jul 2014 (Day 10) as Grade 1. Treatment included fentanyl and tramadol. On 22 Aug 2014 (Day 58), right flank pain improved to Grade 1 and the subject was discharged from the hospital. On 12 Nov 2014 (Day 140), the subject recovered from right flank pain. The Investigator considered right flank pain serious and not related to study drug.

On 04 Feb 2015 (Day 224), tumor response assessment showed disease progression. On 12 Feb 2015 (Day 232), the subject was withdrawn from the study due to disease progression and received the last dose on 11 Feb 2015 (Day 231).

On 01 Sep 2015 (Day 433, 202 days after the last dose), the subject died due to disease progression.

Subject Number	30131001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01403-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Dyspnoea, Vomiting, Nausea

A 33-year-old Asian male was diagnosed with hepatocellular carcinoma on 09 Jul 2013. Significant medical history included increased alpha 1 fetoprotein, hepatic cirrhosis, and cholecystectomy. Previous anticancer therapies included radiotherapy to cervical vertebral lesion (C1 – T1), embolization on cervical mass, hepatectomy, spinal corpectomy, intervertebral disc operation (anterior plating fixation C6 – T1), medical device implantation (mesh cage insertion C7), and transcatheter arterial chemoembolization. Prior and concomitant medications included amlodipine, cefazedone, cefazolin, cefixime, chlorhexidine, eperisone, fentanyl, fluconazole, glucose, hydromorphone, lansoprazole, lidocaine, magnesium hydroxide, metoclopramide, midazolam, naproxen, neoamiyu, ondansetron, ornithine, other emollients and protective (udderly smooth udder cream), oxycodone, paracetamol, pethidine, pregabalin, propofol, ranitidine, smoflipid, targin, tramadol, ursodeoxycholic acid, ventus, vitamins, zaltoprofen, and zinc. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right femur, cervical (C7), lumbar (L1, L4, and L5), and thoracic vertebrae (T6 and T7); lung mass at right lower lobe and multiple pulmonary nodules. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 14 Oct 2013 (Day 1), treatment with study drug was initiated.

On 14 Oct 2013 (Day 1), the subject experienced nausea (Grade 1). On 11 Nov 2013 (Day 29), the event worsened to (Grade 2). On 12 Nov 2013 (Day 30), the subject experienced vomiting (Grade 2). On 25 Nov 2013 (Day 43), the subject was hospitalized for dyspnea (Grade 2), worsening vomiting (Grade 3), and worsening nausea (Grade 3). The subject also experienced ascites (Grade 1). The subject was treated with metoclopramide, ondansetron, glucose, ornithine, vitamins, neoamiyu, smoflipid, lansoprazole, and ranitidine. The study drug was interrupted due to dyspnea, vomiting, and nausea. On 25 Nov 2013 (Day 43), tumor response assessment showed disease progression. On 26 Nov 2013 (Day 44), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 24 Nov 2013 (Day 42). The subject recovered from dyspnea on 26 Nov 2013 (Day 44), and from vomiting on 27 Nov 2013 (Day 45). On 05 Dec 2013 (Day 53), the severity of nausea improved to Grade 1. The subject did not recover from ascites and nausea. The Investigator considered nausea and vomiting serious and possibly related to the study drug; dyspnea serious and not related to the study drug but related to disease progression; ascites nonserious and not related to the study drug.

On 07 May 2014 (Day 206, 164 days after the last dose), the subject died due to disease progression.

Subject Number	30131003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01485-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Pelvic pain
AE(s) Leading to Discontinuation	Proteinuria

A 76-year-old Asian male was diagnosed with hepatocellular carcinoma on 23 Jul 2013. Significant medical history included alcoholic liver cirrhosis, chronic gastritis, benign prostatic hyperplasia, cholecystectomy, chronic cholecystitis, diabetes mellitus, gastroesophageal reflux disease, hypertension, internal hemorrhoids, maculopathy, large intestine polyp, non-alcoholic steatohepatitis, incision site pain (operation site abdomen pain), and large intestinal polypectomy. Previous anticancer therapies included hepatectomy, high frequency ablation, and pulmonary resection. Prior and concomitant medications included ambroxol acefyllinate, amlodipine, doxazosin, glimepiride, glucose, magnesium hydroxide, metformin, natures way primadophilus original, pethidine, ranitidine, tamsulosin, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed mass at right upper lung lobe and multiple lung nodules. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 28 Mar 2014 (Day 1), treatment with study drug was initiated.

On 08 Apr 2014 (Day 12), the subject experienced pelvic pain (Grade 1). On 23 Apr 2014 (Day 27), the pelvic pain was worsened to Grade 2 and the subject was hospitalized. On 24 Apr 2014 (Day 28), bone scan showed mild increase uptake at L4 and L5 vertebral spine and focal increased uptake at right ankle. No treatment was provided and the subject was discharged from the hospital on 25 Apr 2014 (Day 29). On 15 Jun 2014 (Day 80), the severity of pelvic pain improved to Grade 1. On 01 Oct 2014 (Day 188), the subject recovered from pelvic pain. The Investigator considered pelvic pain serious and possibly related to the study drug.

On 10 Apr 2014, (Day 14) subject experienced proteinuria (Grade 2). See table below. On 08 May 2014 (Day 42), the proteinuria worsened to (Grade 3). On 12 May 2014 (Day 46), the study drug was interrupted due to proteinuria. On 15 May 2014 (Day 49), the proteinuria improved to Grade 2. The subject did not recover from proteinuria. On 19 May 2014 (Day 53), the study drug was resumed at the same dose. The Investigator considered proteinuria nonserious and probably related to the study drug.

On 05 Jun 2014 (Day 70), the proteinuria worsened to Grade 3. On 09 Jun 2014 (Day 74), the study drug was interrupted due to this event. On 11 Jun 2014 (Day 76), the proteinuria improved to Grade 2. On 16 Jun 2014 (Day 81), the study drug was resumed at a reduced dose of 8 mg/day due to proteinuria. On 19 Jun 2014 (Day 84), the proteinuria worsened to Grade 3. On 23 Jun 2014 (Day 88), the study drug was interrupted due to this event. On 26 Jun 2014 (Day 91), the proteinuria improved to Grade 2. On 01 Jul 2014 (Day 96), the study drug was resumed at a reduced dose of 4 mg/day due to proteinuria. The subject did not recover from

proteinuria. The Investigator considered proteinuria nonserious and probably related to the study drug.

On 08 Oct 2014 (Day 195), the proteinuria worsened to Grade 3. On 13 Oct 2014 (Day 200), the study drug was interrupted due to this event. On 16 Oct 2014 (Day 203), the proteinuria improved to Grade 2. On 20 Oct 2014 (Day 207), the study drug was resumed at reduced frequency of 4 mg every other day due to proteinuria. On 23 Oct 2014 (Day 210), proteinuria worsened to Grade 3. On 27 Oct 2014 (Day 214), the study drug was interrupted due to this event. On 30 Oct 2014 (Day 217), the subject was withdrawn from the study due to proteinuria. The subject received the last dose of the study drug on 26 Oct 2014 (Day 213). The subject did not recover from proteinuria. The Investigator considered proteinuria nonserious and probably related to the study drug.

On 05 Nov 2014 (Day 223), tumor response assessment showed disease progression.

Table Urine Protein

Laboratory Test Date/Day	**Urine Protein Dipstick**
17 Mar 2014 (Day-11)	negative
28 Mar 2014 (Day 1)	trace
10 Apr 2014 (Day 14)	3+
08 May 2014 (Day 42)	4+
15 May 2014 (Day 49)	3+
05 Jun 2014 (Day 70)	4+
11 Jun 2014 (Day 76)	3+
19 Jun 2014 (Day 84)	3+
26 Jun 2014 (Day 91)	3+
08 Oct 2014 (Day 195)	3+
16 Oct 2014 (Day 203)	2+
23 Oct 2014 (Day 210)	3+

Subject Number	30131004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000221
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Pelvic pain, Oropharyngeal pain, Neck pain

A 43-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Aug 2012. Significant medical history included increased alpha 1 fetoprotein, chronic hepatitis B, hepatic cirrhosis, pancreatitis, splenomegaly, gastroesophageal reflux disease, gastritis, cytomegalovirus colitis, and ulcerative colitis. Previous anticancer therapies included hepatectomy, radiofrequency ablation, and transcatheter arterial chemoembolization. Prior and concomitant medications included alprazolam, amlodipine, azathioprine, cimetropium, contact laxatives, dexamethasone, entecavir, famotidine, glucose, hyaluronidase, infliximab, levobupivacaine, mepivacaine, mesalazine, piprinhydrinate, piroxicam, and ultracet. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at caudate, right, and left lobe of liver and lung mass at left lower lobe of lung, multiple lung nodules, right femur, and right rib mass; MRI showed multiple nodule of the spine (T9, T11, L2, L4, L5, and S1). The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 31 Mar 2014 (Day 5), the subject experienced pelvic pain (Grade 2). The study drug dose did not change. On 21 May 2014 (Day 56), pelvic pain improved to Grade 1. The subject did not recover from this event. The Investigator considered pelvic pain nonserious and possibly related to the study drug.

On 12 Sep 2014 (Day 170), tumor response assessment showed disease progression. On 15 Sep 2014 (Day 173), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on the same day (Day 173).

On 17 Sep 2014 (Day 175), the subject was hospitalized for pelvic pain (pain on left pelvic area; Grade 3) which started as Grade 2 on 05 Sep 2014 (Day 163). The subject was treated with ultracet and radiotherapy to left femur. On 01 Oct 2014 (Day 189), severity of pelvic pain improved to Grade 2. The subject did not recover from this event. The Investigator considered this event serious and not related to the study drug but related to disease progression.

On 05 Oct 2014 (Day 193), the subject was hospitalized for oropharyngeal pain (Grade 2). On 08 Oct 2014 (Day 196), the subject also experienced worsening of neck pain (Grade 3), which started as Grade 2 on 30 Jun 2014 (Day 96) and which prolonged hospitalization. On 08 Oct 2014 (Day 196), CT scan of the neck showed C-spine mass and bone destruction/pharyngeal muscle invasion. The subject was treated with mepivacaine, levobupivacaine, ampicillin/sulbactam, oxycodone, nystatin, cervical epidural block, radiotherapy to C-spine, lumbar spine, and right iliac bone. The subject recovered from the neck pain on 16 Oct 2014 (Day 204) and recovered from oropharyngeal pain on 25 Oct 2014

(Day 213). The Investigator considered neck and oropharyngeal pain serious and not related to the study drug but related to disease progression.

On 31 Dec 2014 (Day 280, 107 days after the last dose), the subject died due to disease progression.

Subject Number	30141001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01466-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Cholecystitis acute
AE(s) Leading to Discontinuation	Proteinuria, Hypertension

An 81-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 May 2012. Significant medical history included benign prostatic hyperplasia, chronic hepatitis C, depression, hypertension, pruritus, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization (6x). Prior and concomitant medications included acetylcysteine, amitriptyline, amlodipine, bepotastine, cefodizime, chlorphenamine, cimetropium, dimeticone, diovan amlo, famotidine, furosemide, haloperidol, hydralazine, hydrocortisone, hydroxyzine, lactulose, lidocaine, lorazepam, megestrol, metronidazole, midazolam, morphine, nicorandil, paracetamol, pethidine, piperacillin/tazobactam, pranlukast, propacetamol, propofol, silybum marianum, tamsulosin, tramadol, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at the right, left, and quadrate lobes of liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

On 11 Nov 2013 (Day 1), treatment with study drug was initiated.

On 14 Mar 2014 (Day 124), the subject was hospitalized for acute calculous cholecystitis (Grade 3) and also experienced proteinuria (Grade 3). The study drug was interrupted due to acute calculous cholecystitis and proteinuria. Abdominal x-ray and CT scan of abdomen showed acute cholecystitis. Laboratory tests showed AST 44 U/L (NR: 7 – 38), ALT 49 U/L (NR: 6 – 42), ALP 173 U/L (NR: 39 – 117), total bilirubin 22.23 umol/L (NR: 5.985 – 22.23), and urine protein dipstick 3+. The subject was treated with pethidine, morphine, tramadol, piperacillin/tazobactam, propacetamol, cefodizime, and metronidazole. On 15 Mar 2014 (Day 125), the subject underwent percutaneous transhepatic gall bladder drainage. On 04 Apr 2014 (Day 145), the subject underwent percutaneous drainage catheter exchange. On 10 Apr 2014 (Day 151), the proteinuria improved to Grade 1 with urine protein dipstick 2+. On 11 Apr 2014 (Day 152), the study drug was resumed at the same dose of 12 mg/day. On 16 Apr 2014 (Day 157), the subject experienced hypertension (Grade 3) with blood pressure of 180/100 mmHg and was treated with diovan amlo, amlodipine, and hydralazine. On 18 Apr 2014 (Day 159), the study drug was interrupted due to hypertension and proteinuria and later that day the subject recovered from hypertension with blood pressure of 140/80 mmHg. On 22 Apr 2014 (Day 163), the subject was withdrawn from the study due to hypertension and proteinuria. The subject received the last dose of the study drug on 17 Apr 2014 (Day 158). On 22 Apr 2014 (Day 163), the subject recovered from acute calculous cholecystitis and from the proteinuria on 07 May 2014 (Day 178). The Investigator considered acute calculous cholecystitis serious and not related to study drug; hypertension nonserious and probably related to study drug; proteinuria nonserious and possibly related to study drug.

On 12 Jan 2015 (Day 428, 270 days after the last dose), the subject died due to disease progression.

Subject Number	30141002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01436-CLI-KR
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy (2x), Oesophageal varices haemorrhage
AE(s) Leading to Discontinuation	Oesophageal varices haemorrhage

A 63-year-old Asian male was diagnosed with hepatocellular carcinoma on 20 Mar 2013. Significant medical history included chronic hepatitis B, esophageal varices, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization (4x). Prior and concomitant medications included amino acids w/carbohydrates, cefodizime, cefotaxime, chlorphenamine, cimetropium, dimeticone, domperidone, entecavir, fentanyl, furosemide, iron, lactulose, lidocaine, metoclopramide, midazolam, ornithine, pantoprazole, paracetamol, pethidine, phytomenadione, propacetamol, propofol, propranolol, rabeprazole, rifaximin, silodosin, spironolactone, terlipressin, tramadol, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe and right pleural mass. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 10 Jan 2014 (Day 1), treatment with study drug was initiated.

On 15 Jan 2014 (Day 6), the subject was hospitalized for hepatic encephalopathy (Grade 3) and also experienced urinary tract infection (Grade 2) with body temperature 38.1 °C. The study drug was interrupted due to hepatic encephalopathy and the subject was treated with lactulose, propacetamol, rifaximin, silodosin, and cefotaxime. Laboratory tests showed AST 194 U/L (NR: 7 – 38), ALP 365 U/L (NR: 39 – 117), and ammonia 67.8205 umol/L (NR: 8.5668 – 47.1174). On 20 Jan 2014 (Day 11), the subject recovered from hepatic encephalopathy and the study drug was resumed at a reduced dose of 8 mg/day due to hepatic encephalopathy. On 23 Jan 2014 (Day 14), the subject recovered from urinary tract infection. The Investigator considered hepatic encephalopathy serious and possibly related to the study drug; urinary tract infection nonserious and not related to the study drug.

On 31 Jan 2014 (Day 22), the subject was hospitalized for hepatic encephalopathy (Grade 3) and esophageal varices hemorrhage (Grade 3) with hematemesis. On the same day (Day 22), the study drug was interrupted due to these events. Laboratory tests showed AST 58 U/L, ALP 187 U/L, ammonia 102.0877 umol/L, Hgb 115 g/L (NR: 120 – 180), INR 1.2 (NR: 0.8 – 1.2), and PT 15.2 sec (NR: 11 – 14.9). On 03 Feb 2014 (Day 25), esophagogastroduodenoscopy confirmed esophageal varices hemorrhage and endoscopic variceal ligation was performed. The subject was treated with lactulose, pantoprazole, iron, cimetropium, terlipressin, and metoclopramide. On the same day (Day 25), the subject recovered from hepatic encephalopathy. On 06 Feb 2014 (Day 28), laboratory tests showed RBC 3.26 x10^12/L (NR: 4 – 5.6), platelet count 91 x10^9/L (NR: 125 – 375), Hgb 90 g/L (NR: 125 – 170), and Hct 0.271 L/L (NR: 0.37 – 0.51). On 09 Feb 2014 (Day 31), the subject was transfused with red blood cell. On 10 Feb 2014 (Day 32), esophagogastroduodenoscopy

showed no signs of active bleeding. On the same day (Day 32), the study drug was resumed at same dose of 8 mg/day. On 13 Feb 2014 (Day 35), esophagogastroduodenoscopy showed another episode of active bleeding and variceal ligation was performed. On the same day (Day 35), the esophageal varices hemorrhage improved to Grade 2. On 13 Feb 2014 (Day 35), the subject was withdrawn from the study due to esophageal varices hemorrhage and received the last dose of the study drug on 12 Feb 2014 (Day 34). On 22 Feb 2014 (Day 44), the subject recovered from esophageal varices hemorrhage. The Investigator considered hepatic encephalopathy and esophageal varices hemorrhage serious and possibly related to the study drug.

On 05 May 2014 (Day 116, 82 days after the last dose), the subject died due to clinical disease progression.

Subject Number	30171005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01516-CLI-KR
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Hypoalbuminaemia

A 54-year-old Asian female was diagnosed with hepatocellular carcinoma on 26 Mar 2014. Significant medical history included abdominal pain, decreased appetite, hepatitis B, hepatic cirrhosis, splenomegaly, and tuberculosis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included alprostadil, cefodizime, chlorphenamine, dexamethasone, folic acid, furosemide, glycerol, godex, human albumin, iron, lactitol, lactulose, lansoprazole, levodropropizine, medilac-s, megestrol, moxifloxacin, oxycodone, paracetamol, pepsane, spironolactone, targin, tenofovir, ultracet, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left lobes of the liver, right and left lower lobe lung masses. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 23 May 2014 (Day 8), the subject experienced an increased blood bilirubin (Grade 3) and bilirubinuria (Grade 2). Laboratory tests showed AST 193 U/L (NR: 10 – 35), ALT 85 U/L (NR: 0 – 35), ALP 1152 U/L (NR: 104 – 338), and total bilirubin 68.4 umol/L (NR: 3.42 – 20.52); urine bilirubin dipstick 2+. On 05 Jun 2014 (Day 21), the subject recovered from bilirubinuria. The subject did not recover from increased blood bilirubin. The Investigator considered increased blood bilirubin nonserious and possibly related to the study drug; bilirubinuria nonserious and not related to study drug but related to disease progression.

On 26 May 2014 (Day 11), tumor response assessment showed disease progression. On 27 May 2014 (Day 12), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on the same day.

On 29 May 2014 (Day 14), the subject was hospitalized for hypoalbuminemia (Grade 2) with symptom of edema. On the same day (Day 14), the severity of increased blood bilirubin improved to Grade 2. Laboratory tests showed albumin 27 g/L (NR: 35 – 55), ALP 392 U/L (NR: 30 – 115), ALT 59 U/L (NR: 10 – 33), AST 115 U/L (NR: 10 – 36), total bilirubin 31.3 umol/L (NR: 1.7 – 18.8), and GGT 168 U/L (NR: 5 – 32). The subject was treated with human albumin, furosemide, and spironolactone. On 09 Jun 2014 (Day 25), the subject recovered from this event with albumin 41 g/L (NR: 38 – 52). On 16 Jun 2014 (Day 32), the severity of increased blood bilirubin worsened to Grade 3 with total bilirubin 165.87 umol/L (NR: 3.42 – 20.52). On 29 Jun 2014 (Day 45), the subject was discharged and did not recover from increased blood bilirubin. The Investigator considered hypoalbuminemia serious and not related to the study drug but related to disease progression; increased blood bilirubin nonserious and not related to the study drug.

On 12 Jul 2014 (Day 58, 46 days after the last dose), the subject died due to disease progression.

Subject Number	30171011
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-013119
Assigned Treatment	Lenvatinib 12 mg/day
Non-Fatal SAE(s)	Lumbar spinal stenosis, Spinal column stenosis

A 67-year-old Asian male was diagnosed with hepatocellular carcinoma on 06 Sep 2006. Significant medical history included allergic rhinitis, anxiety disorder, benign prostatic hyperplasia, spinal osteoarthritis (degenerative spondylosis L-spine), diabetes mellitus, esophageal varices, first degree atrioventricular block, cholelithiasis, gastritis, hepatitis B, hyperlipidemia, hypertension, insomnia, hemorrhoids, chronic gastritis, hepatic cirrhosis, spinal column stenosis, splenomegaly, and urinary calculus. Previous anticancer therapies included radiotherapy to left lobe of liver, transcatheter arterial chemoembolization, doxorubicin, cisplatin, floxuridine, hepatic intra-arterial chemotherapy, and radiofrequency ablation. Prior and concomitant medications included adefovir, amitriptyline, artemisia argyi, atenolol, atorvastatin, barnidipine, bepotastine, bifendate, bromhexine, bupivacaine, buprenorphine, cefazedone, chlorphenamine, cimetidine, cimetropium, clotiazepam, dexamethasone, diclofenac, diosmectite, erdosteine, gallamine, hyaluronidase, ketorolac, lamivudine, levodropropizine, levosulpiride, lidocaine, limaprost, loxoprofen, megestrol, metformin, morphine, other drugs for acid related disorders (cialdine), other drugs for disorders of the musculo-skeletal system (troumin), otilonium, pennel, pepsane, pethidine, prednisolone, rabeprazole, ranitidine, rifaximin, spektramox, telbivudine, tiropramide, tramadol, ursodeoxycholic acid, valsartan, varidase, vitamin B complex, vitamins with minerals, and zaltoprofen. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions in right and left lobes of liver. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 30 Oct 2014 (Day 1), treatment with study drug was initiated.

On 06 Feb 2015 (Day 100), the subject experienced proteinuria (Grade 3) which was ongoing since 23 Dec 2014 (Day 55). Laboratory tests showed 24h urine protein 3.7436 g/24hr and spot protein creatinine ratio 2.5 mg/mg creatinine. On 09 Feb 2015 (Day 103), the study drug was interrupted due to the event. On 11 Feb 2015 (Day 105), the severity of proteinuria improved to Grade 2 with 24h urine protein 1.4708 g/24hr and spot protein creatinine ratio 1.03 mg/mg creatinine. On 16 Feb 2015 (Day 110), the study drug was resumed at a reduced dose of 8 mg/day due to proteinuria. The subject did not recover from proteinuria. The Investigator considered proteinuria nonserious and probably related to the study drug.

On 15 Dec 2015 (Day 412), the subject was hospitalized for worsening of lumbar spinal stenosis (L4 – L5; Grade 3) with symptom of worsening left leg pain. The subject was treated with epidural block, buprenorphine, dexamethasone, hyaluronidase, lidocaine, gallamine, troumin, and cefazedone. The study drug dose did not change. On 21 Dec 2015 (Day 418), the subject recovered from lumbar spinal stenosis. The Investigator considered lumbar spinal stenosis serious and not related to the study drug.

On 18 Jan 2016 (Day 446), tumor response assessment showed disease progression. On 20 Jan 2016 (Day 448), the subject was withdrawn from study due to disease progression and received the last dose of study drug on the same day (Day 448).

On 25 Jan 2016 (Day 453), the subject was hospitalized for spinal column stenosis (Grade 2). The subject was treated with epidural block, bupivacaine, dexamethasone, hyaluronidase, lidocaine, gallamine, troumin, tramadol, and cefazedone. On 26 Jan 2016 (Day 454), the subject recovered from spinal column stenosis. The Investigator considered spinal column stenosis serious and not related to the study drug.

Subject Number	30181003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007339
Assigned Treatment	Lenvatinib 8 mg/day
Non-Fatal SAE(s)	Haemobilia, Decreased appetite, Dyspnoea, Asthenia, Blood bilirubin increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Oedema peripheral

A 68-year-old Asian male was diagnosed with hepatocellular carcinoma on 18 Jul 2013. Significant medical history included hepatitis C, hepatic cirrhosis, and gingival bleeding. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included acetylcysteine, adenosine, alibendol, almagate, amino acids w/electrolytes/glucose, amino acids w/electrolytes/glucose/lipids, anamin, aronamin c plus, cafsol, cebetabs, cefixime, cefodizime, cefotetan, ceftriaxone, chlorphenamine, cimetropium, ciprofloxacin, cough and cold preparations, cough s, dexamethasone, diclofenac, diosmectite, famotidine, fentanyl, folic acid, general nutrients (olive oil + soybean oil), godex, human albumin, hyoscine, iron, l-carbocysteine, lactulose, levothyroxine, lidocaine, livalavin, loperamide, medilac-s, megestrol, meropenem, metoclopramide, midazolam, mosapride, norumo-s, nystatin, otilonium, pamidronic acid, paracetamol, pethidine, phytomenadione, propacetamol, propranolol, ranitidine, remifentanil, sodium chloride, spironolactone, strong hokuphagen, thiamine, tiropramide, tramadol, trimebutine, ultracet, ursodeoxycholic acid, ursofalk+chenofalk, vitamins (tamipool), and zinc. At Screening, tumor assessments via CT scan showed lesion at left liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 07 Mar 2014 (Day 1), treatment with study drug was initiated.

On 28 May 2015 (Day 448), the subject experienced hemobilia (Grade 3) and vomiting (Grade 1). On the same day (Day 448), the subject recovered from vomiting. On 29 May 2015 (Day 449), CT scan of abdomen revealed newly appeared intra hepatic bile ducts and common bile duct dilatation with subtle high density material at common bile duct dilatation suggesting mild biliary obstruction. On 29 May 2015 (Day 449), the subject was hospitalized for hemobilia with severe abdominal pain and experienced decreased weight (Grade 1) with body weight 54.4 kg (Baseline: 59.5 kg). Laboratory tests showed RBC 3.67 x10^12/L (NR: 4 – 5.6) and Hgb 128 g/L (NR: 125 – 170). Treatment included l-carbocysteine, hyoscine, ranitidine, cimetropium, tramadol, ultracet, and ursofalk+chenofalk. The study drug dose did not change. On 02 Jun 2015 (Day 453), endoscopic retrograde cholangiopancreatography confirmed hemobilia and the subject underwent endoscopic papillotomy, hematoma removal in choledochal duct, and endoscopic retrograde biliary stenting (plastic stent). On 03 Jun 2015 (Day 454), the subject was transfused with packed red blood cells to prevent anemia. On 05 Jun 2015 (Day 456), the subject was discharged from the hospital. The subject recovered from hemobilia on 06 Jun 2015 (Day 457). The subject did not recover from decreased weight. The Investigator

considered hemobilia serious and possibly related to study drug; vomiting and decreased weight nonserious and possibly related to study drug.

On 11 Jun 2015 (Day 462), the subject experienced decreased appetite (Grade 2), and the severity of decreased weight worsened to Grade 2 with body weight 52.4 kg. On 16 Jun 2015 (Day 467), the subject experienced dyspnea (Grade 2). On 18 Jun 2015 (Day 469), the subject was hospitalized for dyspnea and decreased appetite. Electrocardiogram was normal, spirometry test was within normal limits, abdominal x-ray showed biliary stent migration, and chest x-ray showed no active disease. Treatment included pamidronic acid, amino acids w/electrolytes/glucose, livalavin, vitamins, zinc, megestrol, and sodium chloride. The study drug dose did not change. On 19 Jun 2015 (Day 470), transthoracic echocardiography report showed relaxation abnormality of left ventricle filling pattern. On 26 Jun 2015 (Day 477), the severity of decreased weight improved to Grade 1 with body weight of 53.8 kg, and the subject recovered from decreased appetite. On the same day (Day 477), the subject was discharged from the hospital. The subject did not recover from dyspnea. The Investigator considered decreased appetite and dyspnea serious and possibly related to study drug; decreased weight nonserious and possibly related to study drug.

On 22 Jul 2015 (Day 503), tumor response assessment showed disease progression. On 04 Aug 2015 (Day 516), the subject was withdrawn from the study due to disease progression and the subject received the last dose of the study drug on the same day.

On 05 Aug 2015 (Day 517), the subject was hospitalized for asthenia (Grade 2). Treatment included amino acids w/electrolytes/glucose, livalavin, strong hokuphagen, vitamins, and anamin. On the same day (Day 517), the severity of decreased weight worsened to Grade 3 with body weight 47.8 kg. On 14 Aug 2015 (Day 526), the subject was discharged from the hospital and was still recovering from asthenia. The subject did not recover from decreased weight. The Investigator considered asthenia serious and possibly related to study drug but related to disease progression; decreased weight nonserious and possibly related to study drug.

On 21 Aug 2015 (Day 533), the subject was hospitalized for blood bilirubin increased (Grade 3), aspartate aminotransferase increased (Grade 3), alanine aminotransferase increased (Grade 2), and peripheral edema (lower extremities; Grade 1). Laboratory tests showed total bilirubin 113.202 umol/L (NR: 3.42 – 20.52), AST 265 U/L (NR: 10 – 40), ALT 172 U/L (NR: 5 – 40), ALP 2920 U/L (NR: 40 – 250), and albumin 23 g/L (NR: 31 – 52). Treatments included livalavin, godex, ursodeoxycholic acid, nystatin, tramadol, lidocaine, propacetamol, cefotetan, ranitidine, and fentanyl. On 22 Aug 2015 (Day 534), bile duct obstruction due to tumor invasion was noted and the subject underwent percutaneous transhepatic bile drainage. On 26 Aug 2015 (Day 538), the subject was transfused with fresh frozen plasma and the subject underwent percutaneous transhepatic bile drainage and drainage catheter tube exchange was done due to decrease in drainage and increase in total bilirubin. On 27 Aug 2015 (Day 539), the subject was transfused with packed red blood cells. On 31 Aug 2015 (Day 543), the subject recovered from alanine aminotransferase increased. Laboratory tests showed ALT 20 U/L, AST 76 U/L, and total bilirubin 113.886 umol/L. On 04 Sep 2015 (Day 547), the subject recovered from peripheral edema. On 17 Sep 2015 (Day 560), the subject was discharged to convalescent hospital. The subject did not recover from blood bilirubin increased and aspartate