Subject Number	12251006
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01503-CLI-JP
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Anaemia

A 67-year-old Japanese male was diagnosed with hepatocellular carcinoma in Feb 2013. Significant medical history included chronic gastritis, cancer pain, large intestine polyp, diabetes mellitus, dysuria, renal impairment, abnormal hepatic function, hypertension, and esophageal varices. Previous anticancer therapies included radiotherapy to sacrum and left lobe liver mass, regional chemotherapy (hepatic intra-arterial chemotherapy), and transcatheter arterial chemoembolization. Prior and concomitant medications included amino acids, amino acids w/electrolytes/glucose/thiamine, ascorbic acid, aspartate calcium, atenolol, betamethasone, calcitriol, carbazochrome, carbohydrates w/potassium chloride/sodium, diazepam, dimeticone, ecabet, esomeprazole, famotidine, flumazenil, furosemide, fursultiamine, general nutrients (nutrition for hepatic insufficiency), heparinoid, human insulin, iron, lidocaine, loxoprofen, magnesium citrate, magnesium oxide, metoclopramide, midazolam, mosapride, neurobion, omeprazole, osmosal, oxycodone, pantethine, pentazocine, polidocanol, pregabalin, prochlorperazine, pronase, rabeprazole, rebamipide, sennoside a+b, silodosin, sodium bicarbonate, sodium phosphate, sodium picosulfate, spironolactone, tamsulosin, timepidium, tranexamic acid, urea, and zoledronic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at left liver lobe; right middle lobe lung mass, and sacral mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 30 Apr 2014 (Day 15), the subject experienced anemia (Grade 2), thrombocytopenia (Grade 2), and upper gastrointestinal hemorrhage (Grade 2) with Hgb 88 g/L (NR: 125 – 170), RBC 2.81 x10^12/L (NR: 4 – 5.6), Hct 0.274 L/L (NR: 0.37 – 0.51), and platelets 73 x10^9/L (NR: 125 – 375). On 11 May 2014 (Day 26), the subject did not take study drug. On 13 May 2014 (Day 28), the subject was hospitalized for worsening of anemia (Grade 3) and thrombocytopenia improved to Grade 1. Repeat laboratory tests showed RBC 2.09 x10^12/L, Hgb 66 g/L (NR: 125 – 170), Hct 0.196 L/L, and platelets 87 x10^9/L. On the same day (Day 28), the study drug remained interrupted due to anemia. On 15 May 2014 (Day 30), gastrointestinal endoscopy showed no active bleeding. The subject was treated with packed red blood cells transfusion, ecabet, rebamipide, ascorbic acid, carbohydrates w/potassium chloride/sodium, omeprazole, iron, esomeprazole, sodium phosphate, general nutrients, neurobion, and amino acids w/electrolytes/glucose/thiamine. On 16 May 2014 (Day 31), colonoscopy showed no bleeding. On 21 May 2014 (Day 36), the capsule endoscopy showed portal hypertensive enteropathy. On 26 May 2014 (Day 41), the subject had double balloon endoscopy and underwent argon plasma coagulation for upper gastrointestinal hemorrhage. On the same day (Day 41), the subject recovered from upper gastrointestinal hemorrhage and on 06 Jun 2014 (Day 52), the subject recovered from thrombocytopenia with platelet count 114 x10^9/L. On 11 Jun 2014 (Day 57), the subject was recovering from anemia with

Hgb 83 g/L (NR: 136 – 170) and was discharged from the hospital. On 29 Aug 2014 (Day 136), the subject recovered from anemia with Hgb 103 g/L (NR: 136 – 170). The Investigator considered anemia serious and probably related to the study drug; upper gastrointestinal hemorrhage nonserious and probably related to the study drug; thrombocytopenia nonserious and possibly related to the study drug.

On 02 Jun 2014 (Day 48), tumor response assessment showed disease progression. On 05 Jun 2014 (Day 51), the subject was withdrawn from study due to disease progression and received the last dose of study drug on 11 May 2014 (Day 26).

On 07 Jan 2015 (Day 267, 241 days after the last dose), the subject died due to disease progression.

Subject Number	12251009
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000777
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Spinal osteoarthritis

A 70-year-old Japanese male was diagnosed with hepatocellular carcinoma on 13 May 2014. Significant medical history included chronic gastritis, cancer pain, constipation, diabetes mellitus, hypertension, insomnia, hepatic cirrhosis, periodontitis, and musculoskeletal pain (shoulder pain). Previous anticancer therapies included radiotherapy to right pelvic lesion and transcatheter arterial chemoembolization. Prior and concomitant medications included alginic acid, amlodipine, aspartate calcium, azilsartan, calcitriol, cefazolin, denosumab, diclofenac, dimeticone, ephedrine, falkamin, famotidine, fentanyl, flurbiprofen, hyzaar, indigo carmine, lidocaine, loxoprofen, magnesium oxide, pentazocine, pronase, propofol, rebamipide, remifentanil, rocuronium, ropivacaine, sennoside a+b, sitagliptin, sodium bicarbonate, super cal, telmisartan, urea, zoledronic acid, and zolpidem. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe; and right pelvic mass. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 08 Oct 2014 (Day 98), the subject was hospitalized to undergo laminoplasty for spinal osteoarthritis (Grade 3), which started on 27 Jun 2014 (Day –6) as Grade 2. The study drug was interrupted due to laminoplasty. On 14 Oct 2014 (Day 104), the subject underwent laminoplasty. After the surgery, the subject experienced wound complication (wound pain; Grade 2). Treatment included loxoprofen, diclofenac, pentazocine, cefazolin, ephedrine, fentanyl, flurbiprofen, lidocaine, propofol, remifentanil, rocuronium, and ropivacaine. On 21 Oct 2014 (Day 111), the subject experienced infusion site swelling (Grade 1). On 22 Oct 2014 (Day 112), the study drug was resumed at same dose. On 24 Oct 2014 (Day 114), the subject recovered from infusion site swelling. On the same day (Day 114), the subject experienced impaired healing (Grade 1). On 28 Oct 2014 (Day 118), spinal osteoarthritis improved to Grade 2 and the subject was discharged from the hospital. On 14 Nov 2014 (Day 135), the subject recovered from wound complication. On 11 Dec 2014 (Day 162), the subject recovered from impaired healing. The subject did not recover from spinal osteoarthritis. The Investigator considered spinal osteoarthritis serious and not related to study drug; impaired healing nonserious and possibly related to study drug; wound complication and infusion site swelling nonserious and not related to study drug.

On 08 Apr 2015 (Day 280), tumor response assessment showed disease progression. On 14 Apr 2015 (Day 286), the subject was withdrawn from the study due to disease progression and received the last dose of study drug on the same day (Day 286).

Subject Number	14021005
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-000442
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Heart valve stenosis

An 82-year-old white female was diagnosed with hepatocellular carcinoma on 05 Jun 2008. Significant medical history included aortic stenosis, dyspnea, hypertension, foot fracture (left foot break), phlebitis, polypectomy, bladder neck suspension (tension free vaginal tape), and urinary incontinence. Previous anticancer therapies included radiotherapy to caudate lobe of liver, hepatectomy, and transcatheter arterial chemoembolization (5x). Prior and concomitant medications included amiodarone, cetirizine, ciprofloxacin, coveram, dexeryl, esomeprazole, furosemide, levocetirizine, loperamide, medicated shampoos (anti-dandruff shampoo), paracetamol, perindopril, and verapamil. 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 15 Sep 2014 (Day 1), treatment with study drug was initiated.

On 04 Sep 2014 (Day –11), electrocardiogram at Screening showed aortic valvular shrinkage but it was not considered clinically significant.

On 19 Sep 2014 (Day 5), the subject experienced heart valve stenosis (Grade 3) with symptoms of dyspnea (Grade 2) and presyncope (Grade 3). On the same day (Day 5), the subject recovered from presyncope. The events of heart valve stenosis and dyspnea were ongoing. The Investigator considered presyncope nonserious and probably related to the study drug.

On 25 Sep 2014 (Day 11), the subject was hospitalized for heart valve stenosis with episode of palpitations and faintness. Clinical examination showed regular heart sounds, murmur of aortic stenosis, and signs of right-sided cardiac decompensation with mild jugular vein distension and hepatojugular reflex. Electrocardiogram showed rhythm characterized by atrioventricular dissociation and QRS widening with left delay indicating accelerated idioventricular rhythm; chest x-ray showed no abnormalities of the pleura or parenchyma; echocardiography showed preserved left ventricular ejection fraction, severe calcific aortic stenosis and a mean pressure gradient of 50 mmHg, moderate mitral stenosis, right chambers were not dilated and contractile, with pulmonary hypertension 40 mmHg. Laboratory tests were done and showed brain natriuretic peptide test 3200 pg/mL (NR: not provided), troponin 16.6 mmol/L (NR: not provided), and D-dimer 422 ng/mL (NR: not provided). The subject was treated with amiodarone. On 26 Sep 2014 (Day 12), the subject experienced second episode of presyncope (Grade 3) and recovered on the same day (Day 12). The study drug was interrupted due to heart valve stenosis, dyspnea, and presyncope. On the same day (Day 12), the subject was diagnosed with ventricular arrhythmia (Grade 3) with heart rate of 82 bpm and QRS interval 124 msec. On 01 Oct 2014 (Day 17), the subject recovered from heart valve stenosis and dyspnea. The subject was discharged from the hospital and the study drug was resumed at a reduced dose of

400 mg/day due to heart valve stenosis. The subject did not recover from ventricular arrhythmia. The Investigator considered heart valve stenosis serious and probably related to study drug; presyncope nonserious and not related to the study drug; dyspnea and ventricular arrhythmia nonserious and probably related to study drug.

On 02 Mar 2015 (Day 169), tumor response assessment showed disease progression and the subject was withdrawn from the study due to disease progression on the same day (Day 169). The subject received the last dose on 01 Mar 2015 (Day 168).

On 31 Aug 2016 (Day 717, 549 days after the last dose), the subject died due to disease progression.

Subject Number	14021016
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-010378
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Atrial fibrillation, Loss of consciousness

A 70-year-old white male was diagnosed with hepatocellular carcinoma on 03 Sep 2014. Significant medical history included alcohol abuse, chronic obstructive pulmonary disease, and phlebectomy (right and left saphenectomia). Previous anticancer therapies included regional chemotherapy (hepatic intra-arterial chemotherapy; 3x). Prior and concomitant medications included amiodarone, amoxicillin, beclometasone, betamethasone, bisoprolol, budesonide, budesonide w/formoterol fumarate, dexeryl, formoterol, furosemide, nebivolol, potassium, ramipril, rivaroxaban, spironolactone, terbutaline, unspecified herbal and traditional medicine (balsamic dye), and verapamil. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 05 Aug 2015 (Day 22), the subject experienced asthenia (Grade 1). On 12 Aug 2015 (Day 29), the subject experienced atrial fibrillation (Grade 3) and hypertension (Grade 1). Vital signs were heart rate 133 bpm and BP 128/89 mmHg. Treatment included rivaroxaban and verapamil. On 26 Aug 2015 (Day 43), hypertension worsened to Grade 2 with BP 139/80 mmHg. On 08 Sep 2015 (Day 56), the subject experienced loss of consciousness (Grade 3) and recovered on the same day (Day 56). On 09 Sep 2015 (Day 57), vital signs were BP 123/93 mmHg, heart rate 125 bpm, and electrocardiogram and echocardiogram confirmed atrial fibrillation with rapid ventricular response. On the same day (Day 57), the study drug was interrupted due to atrial fibrillation and loss of consciousness. On 10 Sep 2015 (Day 58), the subject was hospitalized for atrial fibrillation. Treatment included furosemide, bisoprolol, amiodarone, and nebivolol. On 15 Sep 2015 (Day 63), the subject was discharged from the hospital. On 18 Sep 2015 (Day 66), the subject was re-hospitalized and underwent a cardioversion and recovered from atrial fibrillation. The subject did not recover from asthenia and hypertension. The Investigator considered loss of consciousness serious (important medical event) and possibly related to study drug; atrial fibrillation serious and possibly related to study drug; hypertension and asthenia nonserious and possibly related to study drug.

On 04 Nov 2015 (Day 113), the subject withdrew from the study by choice and received the last dose of study drug on 08 Sep 2015 (Day 56).

Subject Number	14031010
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-007704
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Hepatic encephalopathy

A 76-year-old white female was diagnosed with hepatocellular carcinoma on 07 May 2014. Significant medical history included alcohol use, dyslipidemia, dyspepsia, hypertension, insomnia, constipation, peripheral sensory neuropathy, and hepatic cirrhosis. Previous anticancer therapies included radioembolization (2x). Prior and concomitant medications included celiprolol, dexeryl, econazole, esomeprazole, furosemide, iron, lactulose, lidocaine, paracetamol, pravastatin, sodium bicarbonate, spironolactone, urea, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 6.

On 20 Feb 2015 (Day 1), treatment with study drug was initiated.

On 20 Mar 2015 (Day 29), the subject experienced hyperbilirubinemia (Grade 2) with total bilirubin 49.2 umol/L (NR: 0 – 18.8) and the study drug was interrupted due to the event. On 10 Apr 2015 (Day 50), the study drug was resumed at a reduced dose of 400 mg/day due to hyperbilirubinemia. The subject did not recover from hyperbilirubinemia. The Investigator considered hyperbilirubinemia nonserious and possibly related to the study drug.

On 12 Jun 2015 (Day 113), the subject was hospitalized for hepatic encephalopathy (Grade 2) and study drug was interrupted due to the event. Laboratory tests showed total bilirubin 27 umol/L, AST 52 U/L (NR: 10 – 36), GGT 117 U/L (NR: 5 – 32), ALT and ALP were within normal limits, and albumin 30 g/L (NR: 35 – 55). The subject was treated with lactulose. On 22 Jun 2015 (Day 123), the CT scan of brain showed normal results. On 23 Jun 2015 (Day 124), the subject recovered from hepatic encephalopathy and was discharged from the hospital. On 10 Jul 2015 (Day 141), the study drug was resumed at the same dose. The Investigator considered hepatic encephalopathy serious and possibly related to the study drug.

On 07 Aug 2015 (Day 169), tumor response assessment showed disease progression. On the same day (Day 169), the subject was withdrawn from study due to disease progression and received the last dose of study drug on that day.

On 18 Oct 2015 (Day 241, 72 days after the last dose), the subject died due to disease progression.

Subject Number	14031012
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-006712
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Confusional state

A 47-year-old white male was diagnosed with hepatocellular carcinoma on 19 Aug 2014. Significant medical history included venous malformation, dyspnea, peripheral edema, esophagitis, gastritis, hepatic encephalopathy, hypoglycemic coma, peripheral sensory neuropathy, pulmonary hypertension, and tobacco user. Previous anticancer therapies included hepatectomy and radioembolization. Prior and concomitant medications included cyamemazine, oxazepam, pantoprazole, paracetamol, phytomenadione, pyridoxine, tadalafil, thiamine, and zopiclone. At Screening, tumor assessments of target/non-target lesions via CT scan showed a lesion at right liver lobe; bilateral adrenal masses. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 25 Apr 2015 (Day 30), the subject experienced confusional state (Grade 2). The subject had two episodes of confusion prior to this event within a month that resolved. On 01 May 2015 (Day 36), the subject experienced fatigue (Grade 3). On 07 May 2015 (Day 42), the study drug was interrupted due to fatigue. On 10 May 2015 (Day 45), the subject was hospitalized for confusional state. Treatment included oxazepam, pyridoxine, thiamine, cyamemazine, and phytomenadione. On 11 May 2015 (Day 46), electroencephalogram revealed acute encephalopathy. On 13 May 2015 (Day 48), the nuclear magnetic resonance imaging of brain showed no evidence of lesion or stroke. On 15 May 2015 (Day 50), antineuronal and antiganglioside antibody tests were negative. On 18 May 2015 (Day 53), the subject recovered from confusional state and was discharged from the hospital. The subject did not recover from fatigue. The Investigator considered confusional state serious and probably related to study drug; fatigue nonserious and probably related to study drug.

On 22 May 2015 (Day 57), the subject withdrew from the study by choice and received the last dose of study drug on 06 May 2015 (Day 41).

Subject Number	14061003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-008508
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Ophthalmic herpes simplex

A 74-year-old white male was diagnosed with hepatocellular carcinoma in 2007. Significant medical history included alcoholic cirrhosis, diabetes mellitus, hypertension, insomnia, and sepsis. Previous anticancer therapies included hepatectomy (4x) and radiotherapy to liver. Prior and concomitant medications included aciclovir, allantoin w/amino acids/butyrospermum par (xerial), betadermic, betamethasone, dexamethasone, dexeryl, hexaquine, neodecadron, phenylephrine, racecadotril, ster-dex, tropicamide, valaciclovir, and zolpidem. At Screening, tumor assessments of target/non-target lesions via MRI showed lesions at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 20 Oct 2014 (Day 81), the subject experienced alopecia (Grade 1). On 27 Oct 2014 (Day 88), the subject experienced palmar-plantar erythrodysesthesia syndrome (Grade 2) which started as Grade 1 on 19 Aug 2014 (Day 19). The study drug was interrupted due to both events and the subject was treated with allantoin w/amino acids/butyrospermum par (xerial), betamethasone, betadermic, and dexeryl. On 10 Nov 2014 (Day 102), the subject recovered from palmar-plantar erythrodysesthesia syndrome. On the same day (Day 102), the study drug was resumed at reduced dose of 600 mg/day due to palmar-plantar erythrodysesthesia syndrome. The subject did not recover from alopecia. The Investigator considered palmar-plantar erythrodysesthesia syndrome and alopecia nonserious and probably related to study drug.

On 07 Jul 2015 (Day 341), the subject experienced ophthalmic herpes simplex (Grade 2). Eye examination on 06 Jul 2015 (Day 340) showed stromal keratitis with granulomatous retrodescemetic precipitates and superficial descemetitis (in the sight). On 09 Jul 2015 (Day 343), repeat eye examination revealed very diffuse deep stromal keratitis, more than the lower half of cornea taking the optical axis with diffuse retrodescemetic precipitates (in the sight), significant inflammation of the anterior chamber without hypopyon, clear hyposensitivity, hypertonia at 40 mmHg; and ocular fundus was inaccessible. On 09 Jul 2015 (Day 343), the subject was hospitalized for ophthalmic herpes simplex. The subject was treated with aciclovir and valaciclovir. The study drug dose did not change due to this event. On 12 Jul 2015 (Day 346), the subject was discharged from the hospital. On 21 Aug 2015 (Day 386), the subject recovered from ophthalmic herpes simplex. The Investigator considered ophthalmic herpes simplex serious and not related to study drug.

On 21 Aug 2015 (Day 386), tumor response assessment showed disease progression. However, tumor response assessments on 07 May 2015 (Day 280) and 06 Jul 2015 (Day 340) which were initially assessed as stable disease were changed to disease progression after re-evaluation. On

16 Sep 2015 (Day 412), the subject was withdrawn from the study due to disease progression and the subject received the last dose of study drug on 26 Aug 2015 (Day 391).

Subject Number	14061023
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011816
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Metastases to bone

A 62-year-old white male was diagnosed with hepatocellular carcinoma in 2005. Significant medical history included head injury, hepatitis C, hypertension, and hepatic cirrhosis. Previous anticancer therapies included transcatheter arterial chemoembolization (5x). Prior and concomitant medications included baclofen, enoxaparin, karvea hct, and propranolol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 26 Jun 2015 (Day 1), treatment with study drug was initiated.

On 14 Aug 2015 (Day 50), the subject experienced muscle fatigue (Grade 2) and fatigue (Grade 3) which started as Grade 1 on 10 Jul 2015 (Day 15). On 22 Aug 2015 (Day 58), the study drug was interrupted due to fatigue. On 03 Sep 2015 (Day 70), the subject recovered from fatigue and was recovering from muscle fatigue. On the same day (Day 70), the study drug was resumed at a reduced dose of 600 mg/day due to Investigator's decision. The Investigator considered fatigue and muscle fatigue nonserious and probably related to the study drug.

On 07 Oct 2015 (Day 104), tumor response assessment showed disease progression.

On 28 Oct 2015 (Day 125), the subject was hospitalized for metastases to bone (exploration of metastasis of bone; Grade 2) and the bone biopsy (femoral lesion) on 02 Nov 2015 (Day 130) confirmed bone metastases of hepatocellular carcinoma. The subject underwent osteosynthesis (femoral) and was also treated with radiotherapy. On 13 Nov 2015 (Day 141), the study drug was interrupted due to disease progression. On 26 Nov 2015 (Day 154), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 12 Nov 2015 (Day 140). On 02 Dec 2015 (Day 160), the subject recovered from metastases to bone. The Investigator considered metastases to bone serious and not related to the study drug.

On 18 Oct 2016 (Day 481, 341 days after the last dose), the subject died due to unknown cause.

Subject Number	14101003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-013671
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Anaemia, Pneumothorax traumatic

A 66-year-old white male was diagnosed with hepatocellular carcinoma on 12 Apr 2011. Significant medical history included alcoholism, back pain, benign prostatic hyperplasia, diabetes mellitus, and nephrectomy (right kidney nephrectomy). Previous anticancer therapies included radiotherapy to left liver lobe mass and hepatectomy. Prior and concomitant medications included amphotericin b, augmentin, colecalciferol, dexeryl, diclofenac, furosemide, gliclazide, iron, loperamide, paracetamol, racecadotril, silodosin, spironolactone, and tramadol. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right liver lobe. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

On 23 Jul 2015 (Day 1), treatment with study drug was initiated.

On 04 Jan 2016 (Day 166), the subject experienced anemia (Grade 3) with Hgb 66 g/L (NR: 125 – 170) and RBC 2.67 x10^12/L (NR: 4 – 5.6). The subject was treated with multiple transfusions of packed red blood cells and iron supplements. On 01 Mar 2016 (Day 223), the subject recovered from anemia with Hgb 112 g/L and RBC 3.88 x10^12/L. The Investigator considered the event serious (important medical event) and not related to the study drug.

On 17 Mar 2016 (Day 239), tumor response assessment showed disease progression.

On 20 Mar 2016 (Day 242), the subject was hospitalized for traumatic pneumothorax (related to fall; Grade 3) and also experienced rib fracture (Grade 3). On 21 Mar 2016 (Day 243), the study drug was interrupted due to the traumatic pneumothorax. On 22 Mar 2016 (Day 244), the chest x-ray confirmed traumatic pneumothorax and pneumonia (Grade 2). The subject was treated with paracetamol, augmentin, and colecalciferol. On 29 Mar 2016 (Day 251), the subject recovered from traumatic pneumothorax and pneumonia as confirmed by chest x-ray. On the same day (Day 251), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 20 Mar 2016 (Day 242). The subject was recovering from rib fracture. The Investigator considered traumatic pneumothorax serious and not related to the study drug; rib fracture and pneumonia nonserious and not related to the study drug.

On 18 Jul 2016 (Day 362, 120 days after the last dose), the subject died due to disease progression.

Subject Number	14121001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2014-001084
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Cancer pain, General physical health deterioration
AE(s) Leading to Discontinuation	General physical health deterioration

A 76-year-old white male was diagnosed with hepatocellular carcinoma on 13 Oct 2011. Significant medical history included cancer pain, chronic hepatitis B, chronic kidney disease, inguinal hernia repair, and hypertension. Previous anticancer therapies included regional chemotherapy (4x) and percutaneous ethanol injection therapy. Prior and concomitant medications included amoxicillin, calcium carbonate, colecalciferol, entecavir, fentanyl, hexaquine, lercanidipine, morphine, nadolol, omeprazole, phosphoneurol, pregabalin, and pritorplus. At Screening, tumor assessments of target/non-target lesions via CT showed masses at thoracic vertebra, sternum, and right lower lobe of lung; MRI showed left adrenal mass and lesions at right and quadrate lobes of the liver. The BCLC Stage was C, ECOG performance score was 0, and Child Pugh score was 5.

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

On 20 Oct 2014 (Day –2), the subject was hospitalized for cancer pain (worsening bone metastasis pain; Grade 2). The subject was treated with fentanyl, morphine, and pregabalin. On 23 Oct 2014 (Day 2), the subject recovered from this event. The Investigator considered this event serious and not related to the study drug.

On 20 Nov 2014 (Day 30), the subject experienced asthenia (Grade 2) and decreased appetite (Grade 2). On 24 Nov 2014 (Day 34), the severity of asthenia and decreased appetite improved to Grade 1. On 15 Dec 2014 (Day 55), severity of asthenia worsened to Grade 3. On 17 Dec 2014 (Day 57) the subject recovered from decreased appetite. On 18 Dec 2014 (Day 58), the study drug was interrupted due to asthenia. On the same day (Day 58), tumor response assessment showed disease progression. On 22 Dec 2014 (Day 62), the study drug was resumed at a reduced dose of 400 mg/day due to asthenia. The subject did not recover from asthenia. The Investigator considered asthenia and decreased appetite nonserious and probably related to the study drug.

On 14 Jan 2015 (Day 85), the subject was hospitalized for general physical health deterioration (Grade 3) and the study drug was withdrawn due to this event. On the same day (Day 85), the subject was withdrawn from the study due to disease progression and received the last dose of the study drug on 13 Jan 2015 (Day 84). On 22 Mar 2015 (Day 152, 68 days after the last dose), the subject died due to general physical health deterioration. Autopsy was not performed. The Investigator considered general physical health deterioration serious and not related to the study drug but related to disease progression.

Subject Number	14131002
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-003141
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Pulmonary embolism, Back pain

A 60-year-old white male was diagnosed with hepatocellular carcinoma on 08 Dec 2014. Significant medical history included tobacco poisoning, esophageal varices, hepatitis C, pneumonia, hepatitis non-A non-B, and coronary artery disease. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, amoxicillin, augmentin, carvedilol, general nutrients, lactulose, morphine, oxycodone, panadeine co, paracetamol, prednisolone, tinzaparin, tramadol, and urea. At Screening, tumor assessments of target/non-target lesions via CT scan showed left adrenal mass and liver lesions at segment V and VII. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 08 Jan 2015 (Day 1), treatment with study drug was initiated.

On 13 Jan 2015 (Day 6), the subject was hospitalized for pulmonary embolism (bilateral pulmonary embolism; Grade 3). On 14 Jan 2015 (Day 7), angiogram was abnormal. Treatment included amoxicillin and tinzaparin. On 16 Jan 2015 (Day 9), the subject recovered from the event. The study drug dose did not change. The Investigator considered pulmonary embolism serious and not related to the study drug.

On 21 Jan 2015 (Day 14), the subject experienced asthenia (Grade 3) and decreased appetite (Grade 2). The subject was treated with general nutrients. On 22 Jan 2015 (Day 15), the study drug was reduced to 400 mg every other day due to asthenia. On 09 Feb 2015 (Day 33), asthenia improved to Grade 1. On 23 Feb 2015 (Day 47), the subject recovered from decreased appetite. The Investigator considered decreased appetite nonserious and possibly related to the study drug; asthenia nonserious and not related to the study drug.

On 10 Feb 2015 (Day 34), the study drug dose was increased to 600 mg/day by the Investigator due to improvement in general state of subject. On 24 Feb 2015 (Day 48), the study drug dose was again increased to 800 mg/day by the Investigator due to improvement in general state of subject.

On 05 Mar 2015 (Day 57), the subject was hospitalized for back pain (Grade 3) below the left shoulder blade. Treatment included tramadol, oxycodone, and paracetamol. On 06 Mar 2015 (Day 58), severity of back pain improved to Grade 2. On 11 Mar 2015 (Day 63), the subject experienced disturbance in attention (Grade 2) and respiratory depression (Grade 2) and was diagnosed with accidental overdose (opiates; Grade 2) and recovered on the same day without treatment. On 12 Mar 2015 (Day 64), the study drug was interrupted due to back pain. The subject was treated with morphine. On 18 Mar 2015 (Day 70), the subject recovered from back pain. The Investigator considered back pain serious and not related to the study drug; accidental

overdose, disturbance in attention, and respiratory depression nonserious and not related to the study drug.

On 23 Mar 2015 (Day 75), the study drug was resumed at a reduced dose of 400 mg/day due to improvement in general state of the subject. On 09 Apr 2015 (Day 92), the study drug dose was increased to 600 mg/day by the Investigator due to improvement in general state of the subject.

On 11 May 2015 (Day 124), tumor response assessment showed disease progression and the subject was withdrawn from study due to disease progression. The subject received the last dose of study drug on the same day (Day 124).

On 02 Oct 2015 (Day 268, 144 days after the last dose), the subject died due to disease progression.

Subject Number	15071001
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01401-CLI-IT
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Gastric perforation
AE(s) Leading to Discontinuation	Gastric perforation

A 61-year-old white male was diagnosed with hepatocellular carcinoma on 06 Apr 2004. Significant medical history included gastric ulcer perforation, gastrectomy, typhoid fever, and hepatitis B. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included canrenoic acid, ciprofloxacin, enoxaparin, esomeprazole, furosemide, human albumin, and human erythropoietin. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right liver lobe. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 06 Nov 2013 (Day 1), treatment with study drug was initiated.

On 24 Nov 2013 (Day 19), subject was hospitalized for gastric perforation (Grade 4). On 25 Nov 2013 (Day 20), the subject was withdrawn from the study due to gastric perforation and received the last dose of study drug on 24 Nov 2013 (Day 19). On 25 Nov 2013 (Day 20), the subject underwent gastrorrhaphy with peritoneal lavage and was also treated with canrenoic acid, furosemide, human albumin, ciprofloxacin, and human erythropoietin. On 22 Jan 2014 (Day 78), the subject was discharged from the hospital. On 27 Jan 2014 (Day 83), the subject was readmitted for gastric perforation and was treated with human albumin. On 22 Feb 2014 (Day 109, 90 days after the last dose), the subject died due to gastric perforation. It was unknown if an autopsy was performed. The Investigator considered gastric perforation serious and probably related to study drug. The Investigator stated that it may also be related to previous surgery for gastric perforation about 40 years ago.

Subject Number	15091008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-004590
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Hepatic failure, Myocardial infarction
AE(s) Leading to Discontinuation	Hepatic failure

A 67-year-old white male was diagnosed with hepatocellular carcinoma in Nov 2010. Significant medical history included benign prostatic hyperplasia, type 2 diabetes mellitus, hypertension, and hepatic cirrhosis. Previous anticancer therapies included percutaneous ethanol injection therapy, high frequency ablation (2x), and transcatheter arterial chemoembolization (2x). Prior and concomitant medications included erythromycin, gliclazide, glutathione, insulin glargine, lactulose, liver therapy (kepar: extract of artichoke, thistle, dandelion, turmeric, and commiphora mukul), mesalazine, metformin, methylprednisolone, omeprazole, prednisone, pritorplus, ranitidine, silodosin, telmisartan, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

On 04 Dec 2014 (Day 1), treatment with study drug was initiated.

On 23 Dec 2014 (Day 20), the subject experienced pruritus (Grade 2) and was treated with methylprednisolone and erythromycin. On 02 Jan 2015 (Day 30), the severity of pruritus worsened to Grade 3 and the study drug was interrupted due to this event. On 07 Jan 2015 (Day 35), the subject recovered from pruritus. On 08 Jan 2015 (Day 36), the study drug was resumed at a reduced dose of 400 mg/day due to the event. The Investigator considered pruritus nonserious and possibly related to the study drug.

On 26 Feb 2015 (Day 85), the subject experienced increased alanine aminotransferase (Grade 4), increased aspartate aminotransferase (Grade 4), increased blood alkaline phosphatase (Grade 2), and hepatic failure (Grade 3). Laboratory tests showed ALP 463 U/L (NR: 43 – 115), ALT 1105 U/L (NR: 10 – 40), AST 1065 U/L (NR: 10 – 43), albumin 31 g/L (NR: 35 – 55), total bilirubin 56.6 umol/L (NR: 0 – 18.8), and GGT 808 U/L (NR: 10 – 49). On 27 Feb 2015 (Day 86), the subject experienced increased blood bilirubin (Grade 3) with total bilirubin 63.099 umol/L (NR: 5.13 – 20.52). The study drug was interrupted due to increased aspartate aminotransferase, increased blood alkaline phosphatase, and increased alanine aminotransferase. On same day (Day 86), the subject was withdrawn from the study due to hepatic failure and received the last dose of study drug on 26 Feb 2015 (Day 85). On 02 Mar 2015 (Day 89), the subject was hospitalized for hepatic failure. The subject was treated with glutathione, liver therapy, pritorplus, ranitidine, ursodeoxycholic acid, and methylprednisolone. On 21 Mar 2015 (Day 108), the subject was discharged from the hospital. The subject did not recover from increased aspartate aminotransferase, increased blood alkaline phosphatase, and increased alanine aminotransferase. The outcome of hepatic failure and increased blood bilirubin were unknown. The Investigator considered hepatic failure serious and possibly related to the study drug; increased alanine aminotransferase, increased aspartate

aminotransferase nonserious and probably related to the study drug; increased blood bilirubin and increased blood alkaline phosphatase nonserious and possibly related to the study drug.

On 23 Mar 2015 (Day 110), the subject was hospitalized for left myocardial infarction (Grade 3). No further information was provided. On 22 May 2015 (Day 170), the subject recovered from myocardial infarction. The Investigator considered myocardial infarction serious and not related to study drug.

On 19 Feb 2016 (Day 443, 358 days after the last dose), the subject died and it was unknown if the subject died due to disease progression.

Subject Number	16021003
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01529-CLI-PL
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Anaemia vitamin b12 deficiency, Gastric ulcer haemorrhage, Anaemia

A 75-year-old white female was diagnosed with hepatocellular carcinoma in 2012. Significant medical history included cholecystectomy, chronic gastritis, chronic hepatitis C, hepatitis B, portal hypertension, hepatic cirrhosis, varicose vein operation, esophageal varices, diabetes mellitus, hip arthroplasty (endoprothesis left hip joint), hypertension, hypothyroidism, myocardial ischemia, nephrolithiasis, and hysterectomy. Previous anticancer therapy included hepatectomy. Prior and concomitant medications included acemetacin, aspartic acid, bisoprolol, cyanocobalamin, filgrastim, furosemide, ketoprofen, levothyroxine, meloxicam, metformin, ornithine, pantoprazole, phospholipids, ramipril, and silybum marianum. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 12 Jun 2014 (Day 113), the subject experienced anemia vitamin B12 deficiency (Grade 3). Laboratory tests showed Hgb 77 g/L (NR: 110 – 155), Hct 0.244 L/L (NR: 0.33 – 0.47), and RBC 2.25 x10^12/L (NR: 3.7 – 5.2). On 23 Jun 2014 (Day 124), the subject was hospitalized for anemia vitamin B12 deficiency (Grade 4) with Hgb 74 g/L (NR: not provided). The subject was treated with cyanocobalamin and packed red blood cell transfusion. The study drug dose did not change due to the event. On 25 Jun 2014 (Day 126), the event improved to Grade 2 with Hgb 91 g/L (NR: not provided) and B12 levels 31.32 pmol/L (NR: 138 – 652). On 27 Jun 2014 (Day 128), the subject was discharged from the hospital. On 01 Oct 2014 (Day 224), the subject recovered with sequelae from anemia vitamin B12 deficiency. On 02 Oct 2014 (Day 225), laboratory tests showed RBC 2.93 x10^12/L, Hgb 74 g/L (NR: 110 – 155), and Hct 0.23 L/L. The Investigator considered anemia vitamin B12 deficiency serious and possibly related to study drug.

On 30 Oct 2014 (Day 253), the subject experienced gastric ulcer hemorrhage (Grade 3). Laboratory tests showed RBC 2.64 x10^12/L, Hgb 61 g/L (NR: 110 – 155), and Hct 0.195 L/L. On 03 Nov 2014 (Day 257), the subject was hospitalized for gastric ulcer hemorrhage and treated with pantoprazole and transfused with packed red blood cells. On 07 Nov 2014 (Day 261), upper gastrointestinal tract endoscopy confirmed gastric ulcer hemorrhage. On the same day (Day 261), the subject was discharged from the hospital. The study drug dose did not change due to this event. On 11 Nov 2014 (Day 265), the subject recovered with sequelae from gastric ulcer hemorrhage. The Investigator considered gastric ulcer hemorrhage serious and not related to the study drug.

On 17 Mar 2015 (Day 391), the subject was hospitalized for anemia (Grade 3). Laboratory tests showed Hgb 53 g/L (NR: 120 – 160), Hct 0.189 L/L (NR: 0.36 – 0.46), and RBC 2.61 x10^12/L (NR: 4 – 5.2). The subject was transfused with packed red blood cells. The study drug dose did not change due to this event. On 18 Mar 2015 (Day 392), anemia improved to Grade 1 with Hgb 101 g/L (NR: 120 – 160), Hct 0.342 L/L (NR: 0.36 – 0.46), and RBC 4.3 x10^12/L (NR: 4 – 5.2), and the subject was discharged from the hospital. The subject did not recover from this event. The Investigator considered anemia serious and possibly related to study drug.

On 21 May 2015 (Day 456), anemia worsened to Grade 3 with Hgb 66 g/L (NR: 110 – 155), RBC 2.65 x10^12/L (NR: 3.7 –5.2), and Hct 0.214 L/L (NR: 0.33 – 0.47). On 12 Jun 2015 (Day 478), the study drug was interrupted due to this event. On 20 Jun 2015 (Day 486), the study drug was resumed at the same dose. On 24 Jun 2015 (Day 490), the subject was hospitalized for anemia and was transfused with packed red blood cells. On 25 Jun 2015 (Day 491), anemia improved to Grade 1 with RBC 3.99 x10^12/L (NR: 3.7 – 5.2), Hgb 106 g/L (NR: 110 – 155), and Hct 0.355 L/L (NR: 0.33 – 0.47). The subject did not recover from anemia. The Investigator considered anemia serious and probably related to study drug.

On 10 Dec 2015 (Day 659), the subject experienced leukopenia (Grade 3) with WBC 1.9 x10^9/L (NR: 3.7 – 11). On 07 Jan 2016 (Day 687), subject experienced anemia (Grade 3). Laboratory tests showed Hgb 72 g/L (NR: 110 – 155), RBC 2.68 x10^12/L (NR: 3.7 – 5.2), Hct 0.239 L/L (NR: 0.33 – 0.47), and WBC 1.9 x10^9/L (NR: 3.7 – 11). On 14 Jan 2016 (Day 694), the study drug was reduced to 400 mg/day due to leukopenia. The subject was treated with filgrastim. On 18 Feb 2016 (Day 729), laboratory tests showed WBC 3.6 x10^9/L, RBC 2.55 x10^12/L (NR: 3.7 – 5.2), Hct 0.207 L/L (NR: 0.33 – 0.47), and Hgb 61 g/L (NR: 110 – 155). On 17 Mar 2016 (Day 757), the subject was hospitalized for anemia. On 31 Mar 2016 (Day 771), the subject recovered from anemia with Hgb 127 g/L (NR: 110 – 155), RBC 5.04 x10^12/L (NR: 3.7 – 5.2), and Hct 0.419 L/L (NR: 0.33 – 0.47). On the same day (Day 771), the subject recovered from leukopenia. The Investigator considered anemia serious and probably related to study drug; leukopenia nonserious and probably related to study drug.

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

Subject Number	16021004
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2016-013758
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Gastric haemorrhage

A 68-year-old white female was diagnosed with hepatocellular carcinoma on 10 Nov 2011. Significant medical history included appendectomy, cholecystectomy, chronic hepatitis C, hepatic cirrhosis, portal hypertension, diabetes mellitus, hypertension, myocardial ischemia, intervertebral disc disorder, thyroid cancer, and thyroidectomy. Previous anticancer therapies included transcatheter arterial chemoembolization and hepatectomy. Prior and concomitant medications included akritoin, albumin tannate, bisoprolol, calcium, ciprofloxacin, diclofenac, diprospan, dynamag, ferro-folsan, glimepiride, indapamide, ketoprofen, levothyroxine, meloxicam, metformin, moduretic, ornithine, pantoprazole, ramipril, silybum marianum, spironolactone, tocopherol, and zinc. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at right and left liver lobes. The BCLC Stage was B, ECOG performance score was 0, and Child Pugh score was 5.

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

On 25 Dec 2015 (Day 569), the subject experienced melena (black stools for 5 days; Grade 3). No treatment was provided. On 30 Dec 2015 (Day 574), the subject recovered from the event. The study drug dose did not change. The Investigator considered melena nonserious and not related to the study drug.

On 14 Jan 2016 (Day 589), the subject was hospitalized for gastric hemorrhage (anemia caused by hemorrhage from stomach; Grade 3) with RBC 2.48 x10^12/L (NR: 3.7 – 5.2) and Hgb 64 g/L (NR: 110 – 155). On 19 Jan 2016 (Day 594), the laboratory tests showed iron 28.7 mcg/dL (NR: 45 – 170) and ferritin 23.18 ng/mL (NR: 14 – 233.1). On the same day (Day 594), the subject was transfused with packed red blood cells. On 20 Jan 2016 (Day 595), gastroscopy showed esophageal varices (Grade 1) above the cardia, gastritis (erythematous; Grade 1), reflux gastritis (Grade 1), gastroesophageal heterotopia (gastric heterotopia involving the duodenal bulb; Grade 1), gastric polyps (Grade 1), and duodenal bulb polyp. On the same day (Day 595), histopathological examination of specimen from duodenum, Helicobacter test, and colonoscopy showed no abnormalities. On 21 Jan 2016 (Day 596), the study drug was interrupted due to gastric hemorrhage. The subject was treated with ferro-folsan and pantoprazole. On 29 Jan 2016 (Day 604), the study drug was resumed at the same dose. On 02 May 2016 (Day 698), the subject recovered from gastric hemorrhage. The subject did not recover from reflux gastritis, gastritis, gastric polyps, gastroesophageal heterotopia, and esophageal varices. The Investigator considered the gastric hemorrhage serious and possibly related to the study drug; reflux gastritis, gastritis, gastric polyps, gastroesophageal heterotopia, and esophageal varices nonserious and not related to the study drug.

On 23 Jun 2016 (Day 750), tumor response assessment showed disease progression. On 28 Jul 2016 (Day 785), the subject was withdrawn from study due to disease progression and received the last dose of study drug on the same day (Day 785).

Subject Number	16021017
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011941
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Hepatic failure
AE(s) Leading to Discontinuation	Hepatic failure

A 75-year-old white male was diagnosed with hepatocellular carcinoma on 13 May 2014. Significant medical history included benign prostatic hyperplasia, bilateral cataract operation, diabetes mellitus, hepatitis C, hypertension, hypothyroidism, and hepatic cirrhosis. Previous anticancer therapy included transcatheter arterial chemoembolization. Prior and concomitant medications included asparagine, betaxolol, finasteride, furosemide, levothyroxine, loperamide, magnesium w/vitamin b6, metformin, metoprolol, ornithine, pantoprazole, spironolactone, tamsulosin, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesion at right lobe of liver. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

On 08 May 2015 (Day 1), treatment with study drug was initiated.

On 09 Nov 2015 (Day 186), the subject was hospitalized for hepatic failure (Grade 4) with symptoms of massive pitting peripheral edema, minimal ascites and pleural fluid, weakness, dizziness, yellow skin, yellow eyes, and weight loss of about 10 kg (Baseline: 63.1 kg). The subject also experienced pleural effusion (Grade 2). Doppler ultrasound of the portal system excluded thrombosis. Computerized tomography scan of the pelvis minor showed large volume of fluid in the pelvis minor; chest CT scan with contrast showed minor progression of the focal changes in the abdominal cavity with marked progression of fluid and gastroduodenoscopy showed gastric cardia insufficiency and atrophic gastritis. Blood and pleural fluid cultures and cytological test of pleural fluid showed negative results. The subject was treated with transfusion (fresh frozen plasma), furosemide, and spironolactone. On the same day (Day 186), the subject was withdrawn from the study due to clinical disease progression and received the last dose of study drug on the same day (Day 186). On 11 Nov 2015 (Day 188), laboratory tests showed total bilirubin 182.628 umol/L (NR: 3.42 – 20.52). On 13 Nov 2015 (Day 190), laboratory tests showed AST 82 U/L (NR: 0 – 38) and ALP 69 U/L (NR: 30 – 109). The subject was recovering from hepatic failure and did not recover from pleural effusion. The Investigator considered hepatic failure serious and not related to the study drug but related to disease progression; pleural effusion nonserious and not related to the study drug but related to disease progression.

On 16 Jan 2016 (Day 254, 68 days after the last dose), the subject died due to disease progression.

Subject Number	16021023
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	EC-2015-011052
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Acute myocardial infarction
AE(s) Leading to Discontinuation	Acute myocardial infarction

A 64-year-old white male was diagnosed with hepatocellular carcinoma on 27 Mar 2015. Significant medical history included benign prostatic hyperplasia, large intestinal polypectomy, diabetes mellitus, gastritis, hemorrhoids, hiatus hernia, hypertension, hepatic cirrhosis, anemia, left portal vein thrombosis, and esophageal varices. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included acetylsalicylic acid, carvedilol, clopidogrel, eplerenone, furosemide, gliclazide, pantoprazole, perindopril, potassium, ramipril, simvastatin, spironolactone, torasemide, and ursodeoxycholic acid. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 5.

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

On 06 Oct 2015 (Day 83), the subject was hospitalized for acute myocardial infarction (Grade 4) and pleural effusion (fluid in pleural cavity related to myocardial infarction; Grade 3). Electrocardiogram showed myocardial infarction NSTEMI; chest x-ray revealed shadowing of the right upper and middle pulmonary fields and opacity of the right lower pulmonary field with fluid in the right pleural cavity accompanied by inflammatory/atelectatic lesions. Coronary arteriogram showed 80% stenosis in left anterior descending artery. Laboratory reports showed increased troponin 2389.5 pg/mL (NR: 0 – 34.2) and CRP 68.05 mg/L (NR: 0 – 5). The subject was treated with acetylsalicylic acid, clopidogrel, eplerenone, perindopril, potassium, ramipril, simvastatin, and torasemide. On the same day (Day 83), the subject recovered from acute myocardial infarction with sequelae. On 07 Oct 2015 (Day 84), the echocardiogram revealed segmental contractility impairment, reduced ejection fraction, diastolic dysfunction of the left ventricle, and a moderate probability of pulmonary hypertension. The study drug was withdrawn due to acute myocardial infarction. On 10 Oct 2015 (Day 87), the subject underwent aspiration of pleural cavity. On 14 Oct 2015 (Day 91), ambulatory electrocardiogram showed no ventricular heart rhythm abnormalities. On the same day (Day 91), the subject underwent repeat aspiration of pleural cavity. On 15 Oct 2015 (Day 92), the subject recovered from pleural effusion. On 29 Oct 2015 (Day 106), the subject was withdrawn from the study due to acute myocardial infarction and the subject received the last dose of study drug on 08 Oct 2015 (Day 85). The Investigator considered acute myocardial infarction serious and not related to the study drug; pleural effusion nonserious and not related to the study drug.

On 10 Nov 2015 (Day 118), tumor response assessment showed disease progression.

On 18 Sep 2016 (Day 431, 346 days after the last dose), the subject died due to disease progression.

Subject Number	16031008
Study Name	E7080-G000-304
Eisai Manufacturer's Control Number	E7080-01515-CLI-PL
Assigned Treatment	Sorafenib 800 mg/day
Non-Fatal SAE(s)	Thrombophlebitis superficial

A 65-year-old white male was diagnosed with hepatocellular carcinoma on 05 Feb 2014. Significant medical history included chronic gastritis, cholelithiasis, peripheral venous disease (chronic venous insufficiency of lower limbs), intestinal diverticulum (colon diverticula), diabetes mellitus, hemorrhoids, hypertension, skin necrosis (necrosis of skin of lower left limb), and superficial thrombophlebitis. The subject did not receive any previous anticancer therapies. Prior and concomitant medications included augmentin, calcium chloride, ciprofloxacin, drotaverine, enoxaparin, human mixtard, magnesium sulfate, metformin, metoprolol, omeprazole, ramipril, sodium chloride, tramadol, and trilac. At Screening, tumor assessments of target/non-target lesions via CT scan showed lesions at left and right liver lobes; lymphadenopathies at head of the pancreas, para-caval, inferior vena cava, celiac trunk, and rear lower mediastinum. The BCLC Stage was C, ECOG performance score was 1, and Child Pugh score was 6.

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

On 28 Mar 2014 (Day 15), the subject experienced increased aspartate aminotransferase (Grade 3) which was ongoing since 04 Mar 2014 (Day –10) as Grade 2 and also experienced increased C-reactive protein (Grade 3). Laboratory tests showed AST 368 U/L (NR: 10 – 43), ALT 420 U/L (NR: 10 – 40), ALP 475 U/L (NR: 43 – 115), total bilirubin 31.5 umol/L (NR: 1.7 – 18.8), CRP 210.2 mg/L (NR: 0 – 5), and albumin 24 g/L (NR: 35 – 55). On 11 Apr 2014 (Day 29), the study drug was interrupted due to increased aspartate aminotransferase. On the same day (Day 29), the subject recovered from increased aspartate aminotransferase and experienced decreased performance status (Grade 2). Repeat laboratory test showed AST 175 U/L (NR: 15 – 37). On 22 Apr 2014 (Day 40), the study drug was resumed at reduced dose of 400 mg/day due to decreased performance status. On the same day (Day 40), the subject recovered from decreased performance status. The subject did not recover from increased C-reactive protein. The Investigator considered increased aspartate aminotransferase and increased C-reactive protein nonserious and not related to study drug; decreased performance status nonserious and possibly related to the study drug.

On 09 May 2014 (Day 57), the subject experienced superficial thrombophlebitis (Grade 3). On 22 May 2014 (Day 70), the subject was hospitalized for superficial thrombophlebitis and also experienced pain in extremity (pain of lower extremities; Grade 2). Treatment included augmentin, enoxaparin, sodium chloride, ciprofloxacin, and tramadol. On the same day (Day 70), tumor response assessment showed disease progression. On 23 May 2014 (Day 71), the subject was withdrawn from the study due to disease progression and received the last dose on 16 May 2014 (Day 64). On 26 May 2014 (Day 74), the subject recovered from pain in extremity and did not recover from superficial thrombophlebitis. The Investigator considered