



## Clinical trial results:

### An Open-label, Multi-center, Roll-over Study to Assess Long Term Safety of Lenvatinib Monotherapy or Lenvatinib Combination Regimen or Comparator Treatment arm to Cancer Patients in Eisai Sponsored Lenvatinib Trials

#### Summary

EudraCT number	2017-003668-11
Trial protocol	DE NL ES BE IT RO
Global end of trial date	21 December 2023

#### Results information

Result version number	v1 (current)
This version publication date	29 December 2024
First version publication date	29 December 2024

#### Trial information

##### Trial identification

Sponsor protocol code	E7080-G000-604
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03477175
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Eisai Inc.
Sponsor organisation address	200 Metro Boulevard, New Jersey, United States, 07110
Public contact	EMA Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com
Scientific contact	EMA Medical Information, Eisai Inc., +1 888-274-2378, esi_oncmedinfo@eisai.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 February 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	21 December 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess long-term safety of study drug in subjects who were enrolled in Eisai-sponsored lenvatinib studies.

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following: - Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008) - International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312 - European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states. - Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	China: 19
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	United States: 4

Worldwide total number of subjects	40
EEA total number of subjects	11

Notes:

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### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	13
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Subjects took part in the study at 28 investigative sites in China, United States, Australia, Belgium, Germany, Italy, South Korea, Netherlands, Poland, Romania, and Thailand from 16 August 2018 to 21 December 2023. A total of 40 subjects were screened and enrolled to receive study treatment in this rollover study.

### Pre-assignment

Screening details:

Study consisted of Cohorts A, B and C. However, no subjects met criteria for Cohorts B and C; So, no subjects were enrolled, and no data were collected and reported for these cohorts. As pre-specified in statistical analysis plan, data were collected and reported by regions (China and Rest of World).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort A, China: Lenvatinib Monotherapy

Arm description:

Subjects from China who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 milligram (mg) to 24 mg, capsules, orally until progressive disease (PD), unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib Monotherapy
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenvatinib dose ranging from 4 milligram (mg) to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

<b>Arm title</b>	Cohort A, Rest of the World: Lenvatinib Monotherapy
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Arm description:

Subjects from rest of the world who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-E044-101 [NCT00121719], E7080-A001-109 [NCT02686164], E7080-G000-201 [NCT00784303], E7080-G000-303 [NCT01321554], E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Lenvatinib Monotherapy
Investigational medicinal product code	
Other name	E7080
Pharmaceutical forms	Capsule
Routes of administration	Oral use

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**Dosage and administration details:**

Lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

<b>Number of subjects in period 1</b>	<b>Cohort A, China: Lenvatinib Monotherapy</b>	<b>Cohort A, Rest of the World: Lenvatinib Monotherapy</b>
Started	19	21
Completed	0	0
Not completed	19	21
Consent withdrawn by subject	3	1
Physician decision	1	-
Transitioned to commercial drug	6	6
Adverse event	1	5
Unable to travel due to COVID-19	-	1
Lost to follow-up	1	1
Disease Progression	7	7

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort A, China: Lenvatinib Monotherapy
Reporting group description:	
Subjects from China who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 milligram (mg) to 24 mg, capsules, orally until progressive disease (PD), unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.	
Reporting group title	Cohort A, Rest of the World: Lenvatinib Monotherapy
Reporting group description:	
Subjects from rest of the world who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-E044-101 [NCT00121719], E7080-A001-109 [NCT02686164], E7080-G000-201 [NCT00784303], E7080-G000-303 [NCT01321554], E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.	

Reporting group values	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy	Total
Number of subjects	19	21	40
Age categorical			
Units: subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	11	27
From 65-84 years	3	10	13
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	56.2	62.7	-
standard deviation	± 8.17	± 11.45	-
Sex: Female, Male			
Units: subjects			
Female	9	12	21
Male	10	9	19
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	19	4	23
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	17	17
More than one race	0	0	0

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	19	21	40
Unknown or Not Reported	0	0	0

## End points

### End points reporting groups

Reporting group title	Cohort A, China: Lenvatinib Monotherapy
Reporting group description: Subjects from China who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 milligram (mg) to 24 mg, capsules, orally until progressive disease (PD), unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.	
Reporting group title	Cohort A, Rest of the World: Lenvatinib Monotherapy
Reporting group description: Subjects from rest of the world who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-E044-101 [NCT00121719], E7080-A001-109 [NCT02686164], E7080-G000-201 [NCT00784303], E7080-G000-303 [NCT01321554], E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.	

### Primary: Number of Subjects With any Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects With any Treatment-Emergent Serious Adverse Events (TESAEs) <sup>[1]</sup>
End point description: A treatment-emergent adverse events (TEAE) was defined as an adverse event (AE) that emerged during the treatment in the current roll-over study, having been absent prior to the time the subject signed the current roll-over study informed consent form (ICF), or re-emerged during treatment in the current roll-over study after having been present but resolved before signing the ICF or worsened in severity during treatment in the current roll-over study relative to the pre-ICF state, when the AE was continuous. A serious adverse event (SAE) was any untoward medical occurrence that at any dose: resulted in death; life threatening condition; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; was a congenital anomaly/birth defect or was medically important due to other reasons than the mentioned criteria. Safety analysis set included the group of subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Up to 58.8 months in current study	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned.

End point values	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	7	14		

### Statistical analyses



No statistical analyses for this end point

### Primary: Number of Subjects with Treatment-Related TEAEs

End point title	Number of Subjects with Treatment-Related TEAEs <sup>[2]</sup>
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End point description:

A TEAE was defined as an AE that emerged during the treatment in the current roll-over study, having been absent prior to the time the subject signed the current roll-over study ICF, or re-emerged during treatment in the current roll-over study after having been present but resolved before signing the ICF or worsened in severity during treatment in the current roll-over study relative to the pre-ICF state, when the AE was continuous. Related TEAE was defined as AE with causal relationship between the study drug and the TEAE. Safety analysis set included the group of subjects who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Up to 58.8 months in current study

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned.

End point values	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	15	14		

### Statistical analyses

No statistical analyses for this end point

### Primary: Number of Subjects With any TEAE

End point title	Number of Subjects With any TEAE <sup>[3]</sup>
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End point description:

A TEAE was defined as an AE that emerged during the treatment in the current roll-over study, having been absent prior to the time the subject signed the current roll-over study ICF, or re-emerged during treatment in the current roll-over study after having been present but resolved before signing the ICF or worsened in severity during treatment in the current roll-over study relative to the pre-ICF state, when the AE was continuous. Safety analysis set included the group of subjects who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Up to 58.8 months in current study

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned.

End point values	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	18	20		

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of Subjects With any Non-Serious Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With any Non-Serious Treatment-Emergent Adverse Events (TEAEs) <sup>[4]</sup>
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End point description:

A TEAE was defined as an AE that emerged during the treatment in the current roll-over study, having been absent prior to the time the subject signed the current roll-over study in ICF, or re-emerged during treatment in the current roll-over study after having been present but resolved before signing the ICF or worsened in severity during treatment in the current roll-over study relative to the pre-ICF state, when the AE was continuous. A non-serious TEAE was any AE that was not considered a serious adverse event. Safety analysis set included the group of subjects who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Up to 58.8 months in current study

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data was planned.

End point values	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	18	17		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 58.8 months in current study

Adverse event reporting additional description:

Safety analysis set included the group of subjects who received at least 1 dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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### Reporting groups

Reporting group title	Cohort A, China: Lenvatinib Monotherapy
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Reporting group description:

Subjects from China who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

Reporting group title	Cohort A, Rest of the World: Lenvatinib Monotherapy
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Reporting group description:

Subjects from rest of the world who received lenvatinib monotherapy or who crossed over from a comparator arm to receive lenvatinib monotherapy in their parent study (E7080-E044-101 [NCT00121719], E7080-A001-109 [NCT02686164], E7080-G000-201 [NCT00784303], E7080-G000-303 [NCT01321554], E7080-C086-108 [NCT03009292], or E7080-C086-308 [NCT02966093]) received lenvatinib dose ranging from 4 mg to 24 mg, capsules, orally until PD, unacceptable toxicity, subject's discontinued study, use of nonpermitted concomitant drug, unacceptable noncompliance with the protocol, or lost to follow-up.

Serious adverse events	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 19 (36.84%)	14 / 21 (66.67%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	2	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to lung			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Injury, poisoning and procedural complications			
Spinal compression fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superficial vein thrombosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rotator cuff syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Metabolism and nutrition disorders			
Hypovolaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Cohort A, China: Lenvatinib Monotherapy	Cohort A, Rest of the World: Lenvatinib Monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	17 / 21 (80.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Varicose vein			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	2	2	
Reproductive system and breast disorders			
Vulvovaginal inflammation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	



Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 19 (0.00%)	4 / 21 (19.05%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Hydrothorax			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Investigations			
Amylase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Apolipoprotein A-I decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 19 (21.05%)	1 / 21 (4.76%)	
occurrences (all)	7	1	
Weight decreased			
subjects affected / exposed	0 / 19 (0.00%)	5 / 21 (23.81%)	
occurrences (all)	0	9	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Blood bicarbonate decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Blood creatinine increased		
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)
occurrences (all)	5	3
Blood fibrinogen decreased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Blood thyroid stimulating hormone decreased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Blood urea increased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Gamma-glutamyltransferase increased		
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)
occurrences (all)	7	2
Haematocrit decreased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Haemoglobin decreased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Lipase increased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	2	0
Low density lipoprotein increased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	4	0
Neutrophil count increased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Platelet count increased		
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	0
Platelet-large cell ratio decreased		

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Protein total decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Urinary occult blood positive			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Albumin globulin ratio decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 19 (21.05%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Bile acids increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Hypoaesthesia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Leukocytosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	0 / 21 (0.00%) 0	
Gastrointestinal disorders			
Aphthous ulcer			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	3 / 19 (15.79%)	4 / 21 (19.05%)	
occurrences (all)	17	11	
Gingival disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hepatic function abnormal			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	4 / 19 (21.05%)	0 / 21 (0.00%)	
occurrences (all)	13	0	

Haematuria			
subjects affected / exposed	1 / 19 (5.26%)	3 / 21 (14.29%)	
occurrences (all)	1	4	
Proteinuria			
subjects affected / exposed	6 / 19 (31.58%)	1 / 21 (4.76%)	
occurrences (all)	13	5	
Renal failure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)	3 / 21 (14.29%)	
occurrences (all)	0	3	
Joint effusion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Periarthritis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	5	
Rotator cuff syndrome			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	2	4	
Infections and infestations			
COVID-19			
subjects affected / exposed	4 / 19 (21.05%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Bronchitis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	1	5	
Upper respiratory tract infection			

subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Sinusitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hypercholesterolaemia			
subjects affected / exposed	3 / 19 (15.79%)	0 / 21 (0.00%)	
occurrences (all)	6	0	
Hyperglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hyperlipidaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Hypertriglyceridaemia			
subjects affected / exposed	3 / 19 (15.79%)	0 / 21 (0.00%)	
occurrences (all)	9	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Hypocalcaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	3	0	

Hypochloraemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Hyponatraemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Hypophosphataemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	4	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2018	<p>Amendment 01:</p> <p>The main reason for the protocol amendment is to align the safety data collection in the study with the Food and Drug Administration (FDA) guidance for long-term safety data collection for oncology studies.</p> <ul style="list-style-type: none"><li>Accordingly, the protocol has been updated to define that only treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) will be collected for all subjects.</li><li>It has been clarified that all safety related examinations (including vital signs, physical examination, electrocardiogram [ECG], echocardiogram [ECHO], multigated acquisition scan [MUGA], laboratory investigations should be performed as per local standard of care or as clinically indicated, and should be reported in the case report form (CRF) only if associated with an adverse event (AE/SAE) (ie, only the AE should be recorded in the CRF). Accordingly, all references to these procedures providing specific guidance on conduct of these procedures and statistical reporting in the study were deleted.</li><li>Routine reporting of concomitant medications in the study CRF has been deleted.</li></ul> <p>Other global updates were made to the protocol as follows:</p> <ul style="list-style-type: none"><li>The terminology "study" has been used throughout to replace "trial."</li><li>AE has been updated throughout the protocol to TEAE.</li></ul> <p>Major revisions to individual sections are presented below:</p> <p>The abbreviation list was updated.</p> <p>The approximate number of sites and investigators initially planned for the study was updated from 100 sites and 100 investigators to 50 sites and 50 investigators (Synopsis).</p> <p>The primary objective was harmonized between the Synopsis and Section 8.1, and the term "Eisai-sponsored lenvatinib studies" was harmonized globally in the protocol.</p> <p>The definition of "Parent study" was added in Section 9.1 and the Synopsis.</p>
25 January 2018	<p>Amendment 01 Continued: Figure 1 was updated in Section 9.1 to present all criteria for discontinuation.</p> <p>It was emphasized that the subject will not be without study drug during transition from the parent study to the roll-over study. Also, the timeline of 30 days from termination in the parent study to enrollment in the roll-over study was deleted (Synopsis and Section 9.1)."</p> <p>It was clarified in Section 9.1 and Synopsis that the SAE management and reporting requirements specific to study drugs will be as per the parent study protocol. It was also clarified that ongoing adverse events (AEs) in the parent study will remain ongoing at the time of discontinuation in the parent study, and that the roll-over study will only capture new or worsening TEAEs occurring after signing the ICF for the roll-over study.</p> <p>The number of subjects expected to initially roll over into the study was updated from 200 to 50 in Section 9.3 and Synopsis.</p> <p>Inclusion criterion 2 "Demonstrate compliance with study drug(s), treatment visit schedules, requirements and restrictions listed in the consent form" in Section 9.3.1 and Synopsis was deleted, and the following inclusion criterion was added "Must be able and willing to comply with the current roll-over protocol requirements." All references to parent study protocols being included in the protocol appendices for E7080-G000-604 were deleted since the parent study protocols are not included in the protocol appendices for E7080-G000-604 (Sections 9.1.1, 9.5.9.1, 9.5.9.2, and Synopsis). Added statement that the study drug(s) administered and dispensed (kit number) will be recorded in the CRF (Section 9.4.1 and Section 9.4.4, respectively).</p> <p>Also, the following was added in Section 9.4.1: Subject must not be dispensed more than 2 months supply of study drug(s) at any particular time during participation in Study E7080-G000-604.</p>



25 January 2018	<p>Amendment 01 Continued: Recording in the study of all prior medications administered 30 days before first dose of study drug, any concomitant therapy until 30 days after the final dose of study drug, and any other diagnostic, therapeutic, or surgical procedures relating to malignancy was deleted, and it was clarified that if concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Event CRF (Section 9.4.2.4 [Prior and Concomitant Therapy] and Synopsis).</p> <p>The prohibited concomitant therapies and drugs in Section 9.4.2.6 and Synopsis were harmonized. Also, it was clarified that palliative radiotherapy of painful pre-existing non-target bone metastases will be permitted without being considered progressive disease. This is in line with the current lenvatinib protocols.</p> <p>The requirement for a copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol was deleted since laboratory tests are not mandatory per protocol and will be performed as per local standards or only when clinically indicated [Section 9.4.4 (Drug Supplies and Accountability)].</p> <p>Clarified in Section 9.4.1 and Section 9.2 that subjects rolling over to the study will continue receiving (in addition to lenvatinib or Lenvatinib combination regimen) any other comparator therapy (except placebo). It was also added in Section 9.5.7.1 that, for this study, the study drugs include any other comparator therapy (except placebo) (in addition to lenvatinib or lenvatinib combination therapy).</p> <p>Study assessments:</p> <p>Deleted recording of baseline characteristics, since only demography information will be recorded (Section 9.5.1).</p> <p>Clarified that initial physical examination and any therapeutic area-specific assessments will be performed as per local standard of care or as clinically indicated (Section 9.5.2).</p>
25 January 2018	<p>Amendment 01 Continued: Clarified that tumor assessments will be performed as per local standard of care (Section 9.5.3).</p> <p>Clarified that laboratory parameters, vital signs and physical examination should be performed as per local standard of care or as clinically indicated. Also, added that long term safety information will be collected at the time drug is dispensed to the subject (Section 9.5.7 and Synopsis).</p> <p>Clarified that only TEAEs will be collected in the study and definition of TEAE added (Section 9.5.7.1).</p> <p>Specific guidance and details on conduct of laboratory tests (including the names of the laboratory parameters [formerly Table 2]), procedure for vital signs and weight measurements, conduct of physical examination, and ECG recording was deleted (Sections 9.5.7.5, 9.5.7.6, 9.5.7.7, and 9.5.7.8, respectively, and Synopsis) and it has been mentioned that these procedures and assessments should be performed per local standard of care or as clinically indicated. It was also specified that for vital signs and ECG, only changes from screening vital signs or ECG findings that meet the definition of a TEAE will be recorded on the AE CRF (Section 9.5.7.6 and 9.5.7.8).</p> <p>Table 3 (Schedule of Procedures and Assessments; Section 9.5.8.1) was deleted and replaced with the following statement:</p> <p>All assessments for efficacy and safety will be performed as per local standard of care or as clinically indicated</p> <p>Reasons for discontinuation of the subjects from the study were harmonized between Section 9.1.1, Section 9.5.10, Figure 1 (Section 9.1) and Synopsis.</p> <p>Additional criterion of pregnancy mentioned in Section 9.5.10 was deleted (as it was added in error).</p>

25 January 2018	<p>Amendment 01 Continued: Reporting for TEAEs and SAEs throughout the protocol was harmonized in Sections 9.1, 9.5.7.1, and Synopsis as follows: All TEAEs and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the roll-over study informed consent form (ICF) for up to 28 days after the last dose of study drug(s) (or 5 × half-life of the study drug[s], whichever is longer).</p> <p>Statistical analysis: The study analysis set was updated from the “all treated population” to the “Safety Analysis Set” in Section 9.7 and the Synopsis, and the set was defined as the group of subjects who received at least 1 dose of study drug(s). It was clarified that only demographic characteristics will be reported in the study and “other baseline characteristics” was deleted (Section 9.7.1.3). Former Section 9.7.1.3 (Prior and Concomitant Therapy) was deleted since this data will not be collected in the study. Section 9.7.1.6 (Safety Analyses) was modified to reflect that only TEAE and SAEs will be summarized. Laboratory test results, physical examination findings, vital signs, and echocardiogram results were deleted as these assessments will not be summarized in the study report (also deleted from Section 9.7). Accordingly Section 9.7.1.9 (Laboratory Values), Section 9.7.1.10 (Vital signs), Section 9.7.1.11 (Electrocardiogram), and Section 9.7.1.12 (Other Safety Analyses) were deleted. The definition of TEAE was updated in Section 9.7.1.8 as follows: An AE that emerges during treatment in the roll-over study, having been absent before the time the subject signs the roll-over study ICF or</p> <ul style="list-style-type: none"> <li>• Re-emerges during treatment in the roll-over study, having been present before signing the ICF but stopped before signing the ICF, or</li> <li>• Worsens in severity during treatment in the roll-over study relative to the pre-ICF state, when the AE is continuous.</li> </ul>
25 January 2018	<p>Amendment 01 Continued: It was added that for the TEAEs, the incidence, severity, duration and timing in relation to the start of study medication will be summarized.</p> <p>Since the subjects are not required to adhere to a specific visit schedule, the following sentence was deleted from Section 9.5.10, “All subjects who discontinue the study are to complete the study’ s early discontinuation procedures indicated in the Schedule of Procedures/Assessments found in Table 3.” Also, reasons for discontinuation were added.</p> <p>Section 11.5 (Identification of Source Data): Recording of sampling date and time for drug concentration and sampling date and time for the clinical laboratory test in the CRF was deleted since these procedures will not be done in the study.</p> <p>Appendix 3 – Updated Sponsor’s Grading for Laboratory Values Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 for alkaline phosphatase and γ-glutamyl transpeptidase.</p>
18 October 2018	<p>Amendment 02: Title page: The Investigational New Drug (IND) number was added.</p> <p>Synopsis (Study Design) and Section 9.1: Clarity was added regarding the study design, process of ICF signing, and intention of non-interruption of treatment during a subject’s transitioning from the parent study to Study E7080-G000-604.</p> <p>Section 9.1 (Figure 1): The figure was updated to clarify that the screening period for the study will overlap with the end of the parent study, and accordingly, subjects may remain on the parent study during the screening period. Also, the footnote was updated to state that the Screening Period is “Approximately from Day -30 to Day -1).”</p> <p>Section 9.4.1: It was clarified that subjects must not be dispensed more than a 3-months (formerly, 2 months) supply of study drug(s) at any particular time during participation in this study.</p> <p>Section 9.5.10: Study discontinuation criteria were harmonized with the synopsis.</p> <p>Synopsis (Inclusion Criteria): The statement “Subjects must be rolled over within 30 days of termination from their parent study” was deleted to harmonize with inclusion criteria in the protocol, since this was left in the previous amendment in error.</p> <p>The ICH definition was updated to match the current ICH definition on the title page, abbreviation list, Section 5.2, and investigator signature page.</p>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported