A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma

Registry ID: PHRR160927-001355
Secondary Identification Number: E7080-G000-304; 2013-CT0101

UNIQUE URL

SCIENTIFIC TITLE
A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma

PROJECT DESCRIPTION
This randomized, open-label, multicenter Phase 3 study has been designed to compare the efficacy of Lenvatinib versus Sorafenib as a first-line systemic treatment in subjects with unresectable HCC. Randomization will be used in this study, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Treatments will be open-labeled, since the dosage and administration is different between Lenvatinib and the Sorafenib. Sorafenib is used as a comparator since it is a drug approved for the treatment of unresectable HCC in over 100 countries to date. The dosage of Lenvatinib will be 12 mg or 8 mg QD oral dosing, which is based on the interim efficacy and safety result of a Phase 1/2 clinical study (Study E7080-J081-202). The study sample size is based on the required number of target events to detect the noninferiority and superiority of Lenvatinib to Sorafenib in the comparison of OS. It is estimated that approximately 1450 subjects will be screened and 940 subjects will be randomized and treated with Lenvatinib or Sorafenib at approximately 150 sites in regions that include the Asian-Pacific region and Western regions such as the EU and North America.

NUHRA DETAILS

<table>
<thead>
<tr>
<th>NUHRA Regime</th>
<th>NUHRA Classification</th>
<th>NUHRA Priority</th>
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<tbody>
<tr>
<td>2010 - 2016</td>
<td>Health Technology Development</td>
<td>Drug Discovery and Development</td>
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PROJECT DURATION

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<tr>
<th>Start Date</th>
<th>Duration in Months</th>
<th>Target Completion Date</th>
<th>Actual Completion Date</th>
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<tr>
<td>2014-01-09</td>
<td>13</td>
<td>2015-02-09</td>
<td>2016-01-26</td>
</tr>
</tbody>
</table>

PROJECT STATUS

Contact #: (+632) 8377534, (+632) 8377537, (+632) 8372071-80 loc. 2117, 2112
Email: registry@pchrd.dost.gov.ph
Completed

IMPLEMENTING AGENCY (PRIMARY SPONSOR)

<table>
<thead>
<tr>
<th>Name of Institution</th>
<th>Classification</th>
<th>Region</th>
<th>LTO #</th>
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<tbody>
<tr>
<td>Eisai Co., Ltd.</td>
<td>Private Business</td>
<td>Japan</td>
<td>Not Applicable</td>
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COOPERATING AGENCY (SECONDARY SPONSOR)

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<tr>
<td>Quintiles Philippines, Inc.</td>
<td>Private Business</td>
<td>NCR</td>
<td>CDRR-NCR-CRO-2</td>
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FUNDING AGENCY (SOURCES OF MONETARY OR MATERIAL SUPPORT)

1. Eisai Co., Ltd.

CONTACT FOR PUBLIC QUERIES

<table>
<thead>
<tr>
<th>Name</th>
<th>Email Address</th>
<th>Phone Number</th>
<th>Postal Address</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

CONTACT FOR SCIENTIFIC QUERIES

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<tr>
<th>Name</th>
<th>Email Address</th>
<th>Phone Number</th>
<th>Postal Address</th>
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</thead>
<tbody>
<tr>
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<td><a href="mailto:Daniel_Stepan@eisai.com">Daniel_Stepan@eisai.com</a></td>
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<td>Oncology Business Group Regional Study Director - ‘REFLECT’ - HOPE-304 Study Director, HOPE-218 Eisai Inc. 155 Tice Blvd. Room 3.34 Woodcliff Lake, NJ 07677-8406 USA</td>
</tr>
</tbody>
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INVESTIGATING TEAM

<table>
<thead>
<tr>
<th>Name</th>
<th>Expertise</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marilyn O. Arguillas, MD</td>
<td>Gastroenterology</td>
<td>Davao Doctors Hospital</td>
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<tr>
<td>Arlene Kuan, MD</td>
<td>Gastroenterology</td>
<td>Vicente Sotto Memorial Medical Center</td>
</tr>
<tr>
<td>Judy Lao-Tan, MD</td>
<td>Gastroenterology</td>
<td>Cebu Doctors' University Hospital</td>
</tr>
</tbody>
</table>
HEALTH CONDITION(S) OR PROBLEM(S) STUDIED
Hepatocellular Carcinoma

PRIMARY OUTCOMES
The primary objective of the study is to compare OS in subjects treated with lenvatinib versus sorafenib as a first-line treatment in subjects with unresectable HCC.

KEY SECONDARY OUTCOMES
The secondary objectives of the study are:
- To compare progression-free survival (PFS), time to progression (TTP), and objective response rate (ORR) of subjects treated with lenvatinib versus sorafenib using modified Response Evaluation Criteria in Solid Tumors (mRECIST)
- To compare the impact of treatment on generic Health Related Quality of Life (HRQoL) of subjects treated with lenvatinib versus sorafenib using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and HCC-specific EORTC QLQHCC18 questionnaire
- To compare safety and tolerability of subjects treated with lenvatinib versus sorafenib
- To characterize the pharmacokinetics (PK) of lenvatinib using the population approach
- To assess the PK/pharmacodynamics (PD) relationship between exposure and efficacy/safety

DATE OF FIRST ENROLLMENT
2014-01-09

RECRUITMENT STATUS
Completed

COUNTRIES OF RECRUITMENT
Unspecified

RESEARCH CLASSIFICATION
Clinical Trial

PROJECT LOCATION & INSTITUTIONAL ETHICS REVIEW BOARD WHICH APPROVED THE STUDY

<table>
<thead>
<tr>
<th>Project Location</th>
<th>Institutional Ethics Review Board</th>
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<tbody>
<tr>
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</table>
Davao Doctors Hospital | Davao Doctors Hospital Ethics Review Committee  
Vicente Sotto Memorial Medical Center | Vicente Sotto Memorial Medical Center Ethics Committee  
Cebu Doctors’ University Hospital | Cebu Doctors’ University Hospital Research Ethics Committee (CDUHREC)  
St. Luke’s Medical Center - Quezon City | St. Luke’s Medical Center Institutional Ethics Review Committee  
Veterans Memorial Medical Center | Veterans Memorial Medical Center Ethics Review Committee

FDA DOCUMENT TRACKING NUMBER
2013-1780; 2013-9464; 2013-2364; 2013-2370

FDA / ERC APPROVAL DATE
2013-07-15

AMENDMENT APPROVAL DATES/REASONS
None

KEY INCLUSION AND EXCLUSION CRITERIA (CT)

Inclusion Criteria
1. Subjects must have confirmed diagnosis of unresectable HCC with any of the following criteria:
   - Histologically or cytologically confirmed diagnosis of HCC
   - Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology or with chronic hepatitis B or C infection criteria
2. At least one measurable target lesion according to mRECIST meeting the following criteria:
   - Hepatic lesion
     Ø The lesion can be accurately measured in at least one dimension as ≥ 1.0 cm (viable tumor for typical; and longest diameter for atypical), and
     Ø The lesion is suitable for repeat measurement
   - Nonhepatic lesion
     Ø Lymph node (LN) lesion that measures at least one dimension as ≥ 1.5 cm in the short axis, except for porta hepatitis LN that measures ≥ 2.0 cm in the short axis
Ø Non-nodal lesion that measures ≥ 1.0 cm in the longest diameter Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion.

3. Subjects categorized to stage B (not applicable for transarterial chemoembolization [TACE]) or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system

4. Adequate bone marrow function, defined as:
   - Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L
   - Hemoglobin (Hb) ≥ 8.5 g/dL
   - Platelet count ≥ 75 × 10^9/L

5. Adequate liver function, defined as:
   - Albumin ≥ 2.8 g/dL
   - Bilirubin ≤ 3.0 mg/dL
   - Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) ≤ 5 × the upper limit of normal (ULN)

6. Adequate blood coagulation function, defined as international normalized ratio (INR) ≤ 2.3

7. Adequate renal function defined as creatinine clearance > 40 mL/min calculated per the Cockcroft and Gault formula

8. Adequate pancreatic function, defined as amylase and lipase ≤ 1.5 × ULN

9. Adequately controlled blood pressure (BP) with up to 3 antihypertensive agents, defined as BP ≤150/90 mm Hg at Screening and no change in antihypertensive therapy within 1 week prior to the Cycle1/Dy1.

10. Child-Pugh score A

11. ECOG-PS 0 or 1

12. Survival expectation of 12 weeks or longer after starting study drug

13. Males or females aged at least 18 years (or any age greater than 18 years as determined by country legislation) at the time of informed consent

14. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

15. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic
for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).

16. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

17. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partners must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation). No sperm donation is allowed during the study period and for 30 days after study drug discontinuation.

18. Provide written informed consent

19. Willing and able to comply with all aspects of the protocol

Exclusion Criteria

1. Imaging findings for HCC corresponding to any of the following:
   - HCC with ≥ 50% liver occupation
   - Clear invasion into the bile duct
   - Portal vein invasion at the main portal branch (Vp4)

2. Subjects who have received any systemic chemotherapy, including anti-VEGF therapy, or any systemic investigational anticancer agents, including lenvatinib, for advanced/unresectable HCC. Note: Subjects who have received local hepatic injection chemotherapy are eligible.

3. Subjects who have received any anticancer therapy (including surgery, percutaneous ethanol injection, radio frequency ablation, transarterial [chemo] embolization, hepatic intra-arterial chemotherapy, biological, immunotherapy, hormonal, or radiotherapy) or any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, e.g., granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to randomization

4. Subjects who have not recovered from toxicities as a result of prior anticancer therapy, except alopecia and infertility. Recovery is defined as < Grade 2 severity per Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).
5. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening

6. Prolongation of QTc interval to > 480 ms

7. Gastrointestinal malabsorption or any other condition that might affect the absorption of lenvatinib in the opinion of the investigator

8. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X inhibitors which do not require INR monitoring is permitted. Antiplatelet agents are prohibited throughout the study.

9. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 28 days prior to randomization

10. Gastric or esophageal varices that require active treatment (prophylactic therapy: both interventional and pharmacological is permitted). Patients receiving treatment for active bleeding or require surgical intervention to prevent bleeding are excluded.

11. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months

12. Subjects whose only target lesion(s) is in bone will be excluded

13. Meningeal carcinomatosis

14. Any history of or current brain or subdural metastases

15. Subjects having > 1+ proteinuria on urine dipstick testing will undergo a 24-hour urine collection for quantitative assessment of proteinuria. Subjects with a urine protein ≥ 1 g/24 hours will be ineligible.

16. Surgical arterial-portal venous shunt or arterial-venous shunt

17. Any medical or other condition that in the opinion of the investigator would preclude the subject’s participation in a clinical study

18. Known intolerance to lenvatinib or sorafenib (or any of the excipients)

19. Human immunodeficiency virus (HIV) positive or active infection requiring treatment (except for hepatitis virus)

20. Any history of drug or alcohol dependency or abuse within the prior 6 months

21. Any subject who cannot be evaluated by either triphasic liver CT or triphasic liver MRI because of allergy or other contraindication to both CT and MRI contrast agents

22. Major surgery within 3 weeks prior to randomization or scheduled for surgery during the study
23. Subject has had a liver transplant

**STUDY TYPE**
Interventional

**INTERVENTION NAME**
Lenvatinib

**INTERVENTION DESCRIPTION**
Lenvatinib: 12 mg (or 8 mg) once daily (QD) oral dosing
Sorafenib: 400 mg twice daily (BID) oral dosing

**METHOD OF ALLOCATION**
Randomized

**MASKING / BLINDING**
Open Label

**MASKING DETAILS**
None

**ASSIGNMENT**
Factorial

**PURPOSE**
The primary objective of the study is to compare overall survival (OS) in subjects treated with lenvatinib versus sorafenib as a first-line treatment in subjects with unresectable hepatocellular carcinoma (HCC).

**PHASE**
Phase III

**TARGET SAMPLE SIZE (PHILIPPINES)**
ACTUAL SAMPLE SIZE (PHILIPPINES)
7

REASON FOR THE DIFFERENCE BETWEEN TARGET & ACTUAL SAMPLE SIZES
Recruitment target was not met due to delayed startup of some of the sites.

DATE OF FIRST ENROLLMENT
2014-01-09

RESEARCH UTILIZATION
None