CLINICAL STUDY REPORT ADDENDUM

Name of Company: Eisai Co., Ltd.

Name of Finished Product: Lenvatinib tablets

Name of Active Ingredient: Lenvatinib (E7080)

Study Title

Phase 1/2 Study of E7080 in Patients With Advanced Hepatocellular Carcinoma (HCC)

Investigator(s)/Site(s)

Multicenter: Phase 1: 2 sites in Japan; Phase 2: 12 sites in Japan and 2 sites in Korea (refer to Appendix 16.1.4.1 for the list of investigators and sites)

Study Period

24 Jul 2009 (date of first subject's signed informed consent) to 15 Jun 2014 (date of data cutoff for the primary analysis), and to 13 Aug 2015 (date of the last subject's last visit/last assessment)

Phase of Development

Phase 1/2

Objective(s)

This study determined the MTD in 2 different groups in the Dose Escalation Component (Phase 1) and evaluated the efficacy and safety in the Expansion Component (Phase 2).

Dose Escalation Component (Phase 1):

Primary objective:

To determine the maximum tolerated dose (MTD) as defined by the dose limiting toxicity (DLT) of lenvatinib administered continuously once a day (QD) as 4 weeks cycle in subjects with advanced HCC and hepatic function of Child-Pugh (CP) scores of 5–6 or 7–8

Secondary objectives:

- To evaluate the safety and tolerability of lenvatinib
- To determine the pharmacokinetic (PK) profiles of lenvatinib
- To determine the recommended dose (RD) for future studies
- To evaluate the antitumor efficacy using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (version 1.1 with modification[a])
  - a: Tumor responses were evaluated using RECIST v1.1. The handling of "Not all evaluated" was modified from RECIST v1.1.
- To explore the pharmacodynamic (PD) markers of lenvatinib

Expansion Component (Phase 2):

Primary objective:

To evaluate the efficacy (time to progression [TTP]) and safety of lenvatinib at the recommended dose (RD) in subjects with advanced HCC and hepatic function of CP scores of 5–6

Secondary objectives:

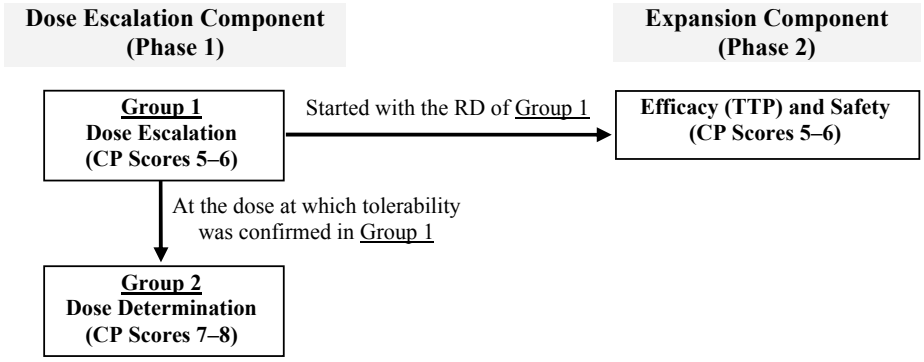
- To evaluate the antitumor efficacy of lenvatinib using mRECIST (version 1.1 with modification[b] for Phase 2) and modified United Nations World Health Organization (WHO) criteria
  - b: To measure target lesions, longest diameters (shorter diameters for lymph node), but not including necrosis, were

measured for the assessment.

- To evaluate the PK profiles of lenvatinib
- To explore the PD markers of lenvatinib

Methodology

This was a multicenter, open-label, Phase 1/2 study of lenvatinib (QD for 28 days per cycle) consisting of a Dose Escalation Component (Phase 1) and an Expansion Component (Phase 2) in subjects with advanced HCC. The Phase 1 part consisted of a dose escalation study in subjects with hepatic function (CP scores of 5–6) (Group 1) and a dose determination study in subjects with CP scores of 7–8 (Group 2). The Phase 2 part was conducted to evaluate the efficacy (TTP) and safety of lenvatinib at the RD of Group 1.



Dose Escalation Component (Phase 1):

The Dose Escalation Component consisted of the Pretreatment Phase, the Treatment Phase, the Extension Phase, Discontinuation, and Follow-up. The Treatment Phase consisted of the first 28-day cycle of treatment, during which subjects were monitored for the development of DLT. Upon discontinuation of lenvatinib, off-study assessments were performed within 7 days of discontinuation. When administration of lenvatinib was discontinued, the follow-up evaluations were performed 30 days after the last lenvatinib administration.

Dose Escalation Scheme in Group 1 (CP Score 5–6):

For Group 1, 6 subjects were to be treated with the lenvatinib starting dose of 12 mg QD. If no more than 1 of 6 subjects had a DLT, the dose was to be escalated to 16 mg QD, and 6 additional subjects were to be treated at this dose. If 2 or more subjects had DLTs at the 12-mg QD dose, then the lenvatinib dose was to be reduced to 8 mg QD in the next cohort of 6 subjects. If the tolerability of the 16-mg QD dose was to be confirmed (no more than 1 subject with a DLT), the dose was to be escalated to 20 mg QD in the next 6 subjects. Further dose escalation or reduction was based on discussions between the sponsor, the investigators, and the medical expert, and if necessary, by an Independent Data Monitoring Committee (IDMC).

The MTD was defined as the highest dose level at which no more than 1 of 6 subjects had a DLT.

Subjects from Group 1 who completed Cycle 1 of treatment were eligible to receive further treatment in the Extension Component of the study.

Dose Determination Scheme in Group 2 (CP Score 7–8):

Group 2 was started after the dose at which tolerability was confirmed in Group 1. The starting dose in Group 2 was the lowest evaluated dose (ie, no more than 1 of 6 subjects with a DLT) in Group 1. Three subjects were enrolled, and if no more than 1 of the 3 subjects had a DLT, at least 3 additional subjects were to be enrolled at the same dose level. If no more than 1 of the 6 subjects had a DLT, the dose was to be escalated to the next dose level that was tolerable in Group 1. If 2 or more of the 6 subjects had DLTs, dose escalation was to be stopped. If 2 or more subjects treated with 12 mg QD had DLTs, the dose was to be reduced to 8 mg QD in the next cohort of subjects. Further dose escalation or reduction was based on discussions between the sponsor, the

investigators, and the medical expert, and, if necessary, by the IDMC.

The MTD was defined as the highest dose level at which no more than 1 of 6 subjects had a DLT.

Expansion Component (Phase 2):

The Expansion Component consisted of the Pretreatment Phase, the Treatment Phase, Discontinuation, and Follow-up. During the Expansion Component, subjects from Group 1 who completed Cycle 1 were treated with the RD that was determined during the Dose Escalation Component (Phase 1). Subjects were treated until disease progression, development of intolerable toxicity, withdrawal of consent, or until discontinuation was judged as necessary by the investigator. An interim evaluation was to be performed at the end of Cycle 2 when tumor response (investigator assessment) would be evaluable for 21 to 23 subjects. If 10 or more subjects had progressive disease (PD) after 2 cycles of treatment, the study was to be discontinued for futility. If less than 10 subjects had PD after 2 treatment cycles, the study continued and additional subjects were enrolled up to a total of 46 subjects.

Number of Subjects (Planned and Enrolled)

Planned:

Dose Escalation Component (Phase 1):

- Group 1: 6 subjects with CP scores of 5–6 per dose level (2–3 dose levels). Minimum 12 subjects; maximum 18.
- Group 2: 3 subjects with CP scores of 7–8 per dose level (1–3 dose levels). Minimum 6 subjects; maximum 18.

Expansion Component (Phase 2):

- 46 subjects with CP scores of 5–6

Enrolled:

Dose Escalation Component (Phase 1):

- Group 1: 9 subjects (6 subjects in the 12 mg cohort, 3 subjects in the 16 mg cohort)
- Group 2: 11 subjects (6 subjects in the 8 mg cohort, 5 subjects in the 12 mg cohort)

Expansion Component (Phase 2):

- 46 subjects (12 mg)

Diagnosis and Main Criteria for Inclusion

Subjects who met all of the following criteria were included in the study.

Dose Escalation Component (Phase 1):

- Male or female patients aged 20 to 80 years at the time of obtaining the informed consent
- Patients with a histologically or clinically confirmed diagnosis of advanced HCC (with typical findings on dynamic computerized tomography [CT]/magnetic resonance imaging [MRI], ie, early phase tumor strain)
  - Primary or recurrent HCC where complete necrosis could not be expected by hepatectomy, local therapies (percutaneous ethanol infusion, radiofrequency ablation, etc), or hepatic artery chemoembolization
  - HCC for which standard therapy was not available or resistant hepatic tumors for which no other appropriate therapy was available
- Patients who met all of the following criteria on laboratory values at the time of screening:
  - Adequate bone marrow function as evidenced by absolute neutrophil count (ANC) $\geq 1.5 \times 10^3/\mu L$, hemoglobin ≥ 9.0 g/dL, and platelet count $\geq 50 \times 10^9/L$

- Adequate liver function as evidenced by serum albumin ≥ 2.8 g/dL, total bilirubin ≤ 3.0 mg/dL, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 times the upper limit of normal (ULN)
- Adequate blood coagulation function as evidenced by prothrombin time ≥ 40% or international normalized ratio (INR) ≤ 2.3
- Adequate renal function as evidenced by serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft and Gault formula
  - Male: (140 – age) × body weight (BW) ÷ (serum creatinine × 72)
  - Female: 0.85 × [(140 – age) × BW ÷ (serum creatinine × 72)]

- Patients with CP scores of 5 to 6 for Group 1 and 7 to 8 for Group 2
- Patients with performance status (PS) of 0 or 1 by Eastern Cooperative Oncology Group (ECOG) criteria
- Patients who had no Grade 2 or higher toxicity caused by prior therapy (except alopecia and toxicities defined by the inclusion/exclusion criteria)
- Patients who agreed to be hospitalized until completion of the Day 1 examination in Cycle 2
- Patients who were expected to survive for 12 weeks or longer after starting lenvatinib
- Patients who gave their written informed consent to participate in this study based on voluntary agreement

Expansion Component (Phase 2):

- Male or female patients aged 20 to 80 years at the time of obtaining the informed consent
- Patients with a histologically or clinically confirmed diagnosis of advanced HCC (with typical findings on dynamic CT/ MRI, ie, early phase tumor strain)
  - Primary or recurrent HCC where complete necrosis could not be expected by hepatectomy, local therapies (percutaneous ethanol infusion, radiofrequency ablation, etc), or hepatic artery chemoembolization
  - HCC for which no other appropriate therapy was available
- Patients who had HCC with at least 1 measurable tumor lesion by RECIST (≥15 mm in the longest diameter for nonlymph node and ≥ 20 mm in the short-axis diameter for lymph node) and with any of the following:
  - One to 3 tumor lesions with > 3 cm diameter (if only 1 lesion, > 5 cm diameter)
  - Four or more tumor lesions
  - Portal vein invasion of Vp1 or Vp2
  - Extrahepatic spread
- Patients who met all of the following criteria on laboratory values at the time of screening:
  - Adequate bone marrow function as evidenced by ANC ≥ 1.5×10^3/μL, hemoglobin ≥ 9.0 g/dL, and platelet count ≥ 50×10^9/L
  - Adequate liver function as evidenced by serum albumin ≥ 2.8 g/dL, total bilirubin ≤ 3.0 mg/dL, and ALT and AST ≤ 5 times ULN
  - Adequate blood coagulation function as evidenced by prothrombin time ≥ 40% or INR ≤ 2.3
  - Adequate renal function as evidenced by serum creatinine ≤ 2.0 mg/dL or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft and Gault formula
    - Male: (140 – age) × BW ÷ (serum creatinine × 72)
    - Female: 0.85 × [(140 – age) × BW ÷ (serum creatinine × 72)]
- Patients with CP scores of 5 to 6
- Patients with PS of 0 or 1 by ECOG criteria
- Patients who had no Grade 2 or higher toxicity caused by prior therapy (except alopecia and toxicities

defined by the inclusion/exclusion criteria)

- Patients who were expected to survive for 12 weeks or longer after starting lenvatinib
- Patients who gave their written informed consent to participate in this study based on voluntary agreement

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Lenvatinib tablets 4 mg were administered orally QD in the morning (without regard to food intake) in continuous 4-week (28-day) cycles. Dose reduction or interruption was allowed for subjects who experienced lenvatinib-related toxicity.

Lenvatinib was self-administered orally by the subject. The 8, 12, and 16 mg doses consisted of two 4-mg tablets, three 4-mg tablets, and four 4-mg tablets, respectively. The lot numbers of product used in this study include:

- P85007ZZB (1 mg tablets)[a]
- P85010ZZA, P88013ZZA, P04016ZZD, P37004ZZB[b] (4 mg tablets in Japan)
- P88013ZZB, P04016ZZE (4 mg tablets in Korea)

a: In this study, only lenvatinib 8 mg (two 4 mg tablets QD), 12 mg (three 4 mg tablets QD), or 16 mg (four 4 mg tablets QD) was administered and there was no need to use 1 mg tablets (eg, lenvatinib 10 mg). Therefore the 1-mg tablets (P85007ZZB) were not shipped to the clinical site and were not used during the study.

b: The expiry date for lenvatinib 4-mg tablets (P04016ZZD) was March 2014 and there was one subject (Subject ID: PPD who was still receiving study drug. Therefore the 4-mg tablets (P37004ZZB) were packaged in a bottle (30 tablets per bottle) instead of press through package (PTP) and were shipped to the clinical site on 04 Feb 2014.

A list of subjects receiving each study drug lot number is provided in Appendix 16.1.6. No additional lots were used after the data cutoff date (15 Jun 2014).

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Not applicable

Duration of Treatment

Subjects continued study treatment as long as the criterion for discontinuation in an individual subjects was not met. Subjects attended a final study visit within 30 days from discontinuation of study treatment.

Assessments

Efficacy

In the Dose Escalation Component (Phase 1), tumor assessments were performed using RECIST 1.1. Tumor response of subjects who had a measurable tumor lesion at screening was evaluated based on RECIST 1.1 every 8 weeks (±1 week) from the first day of lenvatinib administration. Efficacy assessments in Phase 1 were as follows:

- Tumor assessments (target lesion, nontarget lesion, and presence/absence of new lesion): when tumor measurement was possible, tumor lesion was assessed according to the RECIST 1.1

In the Expansion Component (Phase 2), tumor assessments were performed using mRECIST, RECIST 1.1, and WHO criteria. Tumor lesions (CR/PR/SD/PD/NE) were evaluated by the investigators and Independent Radiologic Review Committee (IRRC). Efficacy assessments in Phase 2 were as follows:

- Time to progression (TTP): defined as the time from the date of registration to the date when progressive disease was first confirmed. Progressive disease was to be evaluated according to mRECIST by an independent imaging review.

- Progression-free survival (PFS): defined as the time from the date of registration until the date when progressive disease was first confirmed or death (whichever occurred first)
- Objective response rate (ORR): defined as the proportion of subjects who achieved a tumor response of complete response (CR) plus partial response (PR)
- Disease control rate (DCR): defined as the proportion of subjects who achieved a tumor response of CR + PR + stable disease (SD). DCR was to be evaluated at 8 weeks and at 16 weeks in this study.
- Overall survival (OS): defined as the time from the date of registration until the date of death

The following evaluations were performed every 8 weeks (±1 week) from the first day of lenvatinib administration.

- CT for lesions from lung to pelvis and other lesions where tumor was suspected (MRI could be used only for head and neck lesions)
- Liver dynamic CT (precontrast, artery-dominant phase, and equilibrium phase)
- Bone scintillation or x-ray if bone metastases were suspected

Pharmacokinetics

- Plasma concentration of analytes (unchanged lenvatinib) was determined

Pharmacodynamics

Blood samples were taken and plasma concentrations of lenvatinib were measured. The following PD markers were measured and changes in PD markers were analyzed for exploratory purposes.

- Angiogenesis markers in plasma
- Circulating endothelial cells (CECs) (Dose Escalation Component [Phase 1] only)

Pharmacogenomics

Pre- and posttreatment changes in mRNA expressions such as CD34 which correlated with circulating endothelial cell count. The mRNA was measured using peripheral blood samples of subjects who consented for gene analysis of mRNA markers.

Safety

The safety profile was assessed by monitoring and recording all adverse events (AEs) (according to the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0), clinical laboratory tests (eg, hematology, blood biochemistry, blood coagulation, urinalysis), vital signs (systolic/diastolic BP, pulse rate, body temperature) and body weight, electrocardiogram (ECG), and other special tests (ECOG-PS, CP score, and pregnancy test).

In the Dose Escalation Component (Phase 1) only, MTD defined by DLT was determined. A DLT was defined as any of the following:

- Any Grade 4 or higher hematologic toxicity or Grade 3 thrombocytopenia that required blood transfusion
- Any Grade 3 or higher nonhematologic toxicity:
  - Abnormal clinical laboratory values that required no treatment was not considered a DLT.
  - Hypertension that was Grade 4 hypertension uncontrolled by antihypertensive drug(s) was considered a DLT.
  - Aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 10.0 × ULN was to be considered a DLT.
  - Proteinuria 4+ by urine dipstick was a DLT. Grade 3 proteinurea by dipstick alone was not a DLT. Proteinuria 3+ by urine dipstick was to be monitored by 24-hour urine collection. Proteinuria >3.5 g

for 24 hours was to be considered a DLT.

- Diarrhea/vomiting/nausea that was managed with supportive therapies was not considered a DLT. Diarrhea/vomiting/nausea of Grade 3 or higher that was uncontrollable despite maximal supportive therapies was to be considered a DLT.

- When the number of doses administered during the first cycle fell below 75% of the prescribed number of doses due to the occurrence of toxicity (rather than due to progression or some other reason)

Safety parameters were continually monitored from informed consent to study termination. Results of intensive ECG monitoring using triplicate 12-lead ECGs were collected at screening and once in every cycle.

Bioanalytical Methods

Lenvatinib was quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method. Before the analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility were documented.

Tables and Subject Data Listings for This Clinical Study Report Addendum

The clinical study report of this study was already finalized on 10 Apr 2015 based on the cutoff data as of 15 Jun 2014. For this clinical study report addendum, data for subject disposition were summarized. Treatment-emergent adverse events reported during the entire study were to be listed for the 1 subject (Subject PPD who was still on study treatment at the cutoff date. Along with the correction of the database for the original clinical study report, summary of treatment compliance for lenvatinib was updated.

Sample Size Rationale

In the Dose Escalation Component (Phase 1), the target enrollments per site were 6 to 9 subjects for Group 1 and 3 to 9 subjects for Group 2. The major objective of this Component was the assessment of the safety and tolerability of lenvatinib. Considering this, no clinical hypothesis or assessment criteria had been specified and the sample size for this Component was not based on statistical criteria. Dose group sizes of 3 to 6 subjects were considered adequate to address initial assessment of safety to support dose escalation.

In the Expansion Component (Phase 2), sample size for this Component was determined using the following algorithm:

H_0: $\lambda = \log 2/MTTP_0$, H_A: $\lambda = \log 2/MTTP_1$

Where exponential distribution was assumed for TTP and λ was used as a parameter showing the hazard of progressive disease. $MTTP_0$ and $MTTP_1$ show medians of threshold and expected TTP, respectively, and have been set as 2.7 months and 4.1 months referring to the results of the subgroup analysis in the SHARP study, respectively (Sherman, et al., 2008). Under H_A, assuming the probability that the lower limit of the 2-sided 90% CI for MTTP exceeds $MTTP_0$ is more than 80%, the number of required events is 36 and the number of required subjects is 41 when the registration period is 12 months and the follow-up period is 6 months. Estimating that approximately 10% of subjects were eliminated from analysis, the target sample size was set at 46.

Study Status

Dose Escalation Component (Phase 1)

Not applicable.

Expansion Component (Phase 2):

The data cutoff date for the clinical study report was 15 Jun 2014, with a completed clinical study report on 10 Apr 2015. One subject (Subject PPD in the Expansion Component [Phase 2]) was still on study treatment at the data cutoff (15 Jun 2014). The subject discontinued the study treatment due to disease progression and received lenvatinib for a total of 1511 days. This clinical study report addendum presents several listings (eg, dosing and extent of exposure, tumor assessment, adverse event, laboratory, vital signs [see. Appendix 16.2]) for the subject including the follow-up data up to the last subject's last assessment as of 13 Aug 2015.

The additional safety results on this addendum identify no new safety concerns and do not alter the conclusions of the original clinical study report.

Subject Disposition/Analysis Sets

A total of 46 subjects were eligible to continue in the study. The Enrolled Analysis Set was comprised of these subjects. In this study, the Safety Analysis Set, the FAS, the PK Analysis Set, and the PD Analysis Set were identical (the number of subjects was 46). The Per Protocol Set (PPS) excluded 5 subjects and comprised 41 subjects. Subject PPD was included in PPS.

Discontinuations from Study Treatment

See Table 1. Subject PPD discontinued the study treatment due to disease progression.

Treatment Compliance for Lenvatinib

A summary of administration of lenvatinib for the FAS and the PPS is presented in Table 2.

Efficacy, Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

Not applicable.

Fatal Adverse Events

No fatal TEAEs were reported after the cutoff date.

Serious Adverse Events

No serious adverse events were reported after the cutoff date.

Treatment-Emergent Adverse Events

Two TEAEs that occurred or aggravated after the cutoff date were reported for Subject PPD (Table 4). Table 14.3.1.2.2.4, Table 14.3.1.2.2.8, and Table 14.3.1.2.2.16 were updated.

- Gastritis atrophic (1 event), Grade 2, Not related, Not recovered
- Rash (1 event), Grade 2, Not related, Not recovered

Rash was included in TEAEs occurring in at least 10% of subjects overall, therefore Table 3 was also updated.

Treatment-Emergent Adverse Events Leading to Study Drug Interruption

Four additional events of proteinuria were reported for Subject PPD (Table 5). Table 14.3.2.2.5 was updated.

Date of Report

16 Dec 2015