**REFLECT TRIAL** *(STUDY 304): PHASE 3 TRIAL OF LENVATINIB vs SORAFENIB IN UNRESECTABLE HEPATOCELLULAR CARCINOMA (uHCC)*

Sponsor: Eisai Co., Ltd., Eisai Inc., and Eisai Ltd

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**Background and Rationale**

Lenvima is not approved for HCC. This document discusses an investigational use for an FDA-approved product. It is not intended to convey conclusions about efficacy and safety. There is no guarantee that any investigational uses of FDA-approved products will successfully complete clinical development or gain FDA approval.

**uHCC** is an advanced type of liver cancer that develops in the tissue of the liver as either a single tumor or as multiple small tumors throughout the liver and cannot be removed by surgery.

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor shown to inhibit activities of certain receptors associated with angiogenesis and tumor growth, including VEGFR 1-3, PDGFRα, KIT and RET. Lenvatinib also inhibits fibroblast growth factor (FGF) receptors FGFR 1, 2, 3 and 4.

**Phase 2 study**

In a Phase 2 study, lenvatinib was evaluated in 46 patients with advanced HCC in Japan and Korea who did not qualify for surgical resection or local therapies. Patients received lenvatinib at a dosage of 12 mg once daily in 28-day cycles.

The efficacy and safety results from this trial encouraged further study of lenvatinib in this patient population and led to the initiation of Study 304.

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### Key eligibility criteria *(N=954)*

- Confirmed unresectable HCC
- Measurable disease by mRECIST
- Barcelona Clinic Liver Cancer Stage B or C
- Child-Pugh score A
- ECOG PS: 0 or 1
- No prior systemic anticancer agents
- ≤50% liver occupation

### Stratification

- Geographic region
- Macroscopic portal vein invasion or extrahepatic spread or both (No/Yes)
- ECOG (0/1)
- Body weight (<60 kg/≥ 60 kg)

### Patient population:

The trial was conducted in

- **21 COUNTRIES**
- **WITH 954 PATIENTS**
- **AT 183 TRIAL SITES**

### Primary endpoint:

- **Overall survival:** Length of time from the date of randomization until death

### Secondary endpoints:

Endpoints evaluated using mRECIST and determined by investigator assessment. Independent review is ongoing.

- **Progression-free survival:** Length of time from the date of randomization until disease progression or death
- **Time to progression:** Length of time from the date of randomization until disease progression
- **Objective response rate:** Sum of partial responses plus complete responses; partial response being at least a 30% decrease in the sum of diameters of viable target lesions based on mRECIST
- **Quality of life**
- **Plasma pharmacokinetics parameters**

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