1 ABSTRACT

1.1 Study Title

A Multicentre, Observational, Phase 4 Study to Evaluate the Safety and Tolerability of Lenvatinib in Patients With Advanced or Unresectable Hepatocellular Carcinoma (STELLAR)

Version date: 14 Jun 2024

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1.2 Keywords

Hepatocellular carcinoma; safety; non-interventional; observational

1.3 Rationale and Background

Study E7080-M000-508 (hereafter referred to as Study 508) was a prospective, non-interventional post-marketing (Category 3) Phase 4 study requested by the Committee for Medicinal Products for Human Use (CHMP) during the assessment of lenvatinib for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy, in order to 'characterise hepatic-related toxicity and overall safety profile (SAEs, Grade 3 to 5 AEs, dose modifications and discontinuations due to AEs) in real-life conditions in the EU (Western population) in HCC patients, including in patients with Child-Pugh B' (procedure number EMEA/H/C/003727/II/0011/G). In accordance with the Agency's request during review of the Study 508 protocol, the study included a cohort of patients treated with sorafenib as an 'internal calibration'. Of note, sorafenib is approved for the treatment of HCC in Europe in any line of therapy.

On 15 Nov 2022, Eisai discussed Study 508 enrollment status with the Agency and highlighted the challenges of completing the study in a timeframe that would enable clinically meaningful data to be available for patients and prescribers. These study challenges were acknowledged by the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur, and it was agreed that an interim report from this study could be submitted as a component of a Type II variation to support characterisation of lenvatinib-related hepatotoxicity.

The Study 508 interim report, dated 26 Jul 2023, presented the data for 149 lenvatinib-treated patients and 93 sorafenib-treated patients and was submitted with the Type II variation

(EMEA/H/C/003727/II/0053) 10 Aug 2023. The submission included the agreed upon analysis of pooled safety data from lenvatinib-treated Western patients with HCC in 2 real-world studies: Study 508 and ELEVATOR, and 2 randomized, controlled trials: E7080-G000-304/REFLECT (Study 304) and E7080-G000-311. Based on review of the results of the interim analysis of study data, together with the pooled safety analysis, the EMA concluded that no new safety or efficacy concerns had been demonstrated for the approved indication of lenvatinib in the treatment of patients with HCC (positive CHMP opinion received 30 Nov 2023) and agreed the study could be closed. Subsequently, clinical study investigators were informed that the study had met its objectives, and the study was to be closed to enrollment 13 Dec 2023; in actuality, the last patient was enrolled 27 Sep 2023.

This final report is focused on data relating to the primary objectives of Study 508 (ie, characterisation of lenvatinib-related hepatotoxicity and the overall safety profile of lenvatinib in HCC) and related secondary endpoints, to assess any differences in the real-world safety profile and efficacy (overall survival [OS]) of lenvatinib in HCC. Safety data for sorafenib are included as an 'internal calibration', as requested by the Agency.

1.4 Research Question and Objectives

Primary objectives:

- To further characterise hepatotoxicity in patients with advanced or unresectable HCC treated with lenvatinib.
- To further characterise the overall safety profile (serious adverse events [SAEs], Grade 3 to 5 adverse events [AEs], dose modifications and discontinuations due to AEs) in patients with advanced or unresectable HCC treated with lenvatinib.

Secondary objectives:

- To assess treatment patterns (eg, treatment duration, incidence of dose interruptions, dose reductions, relative dose intensity, treatment sequencing) in patients with advanced or unresectable HCC treated with lenvatinib.
- To assess OS in patients with advanced or unresectable HCC treated with lenvatinib.
- To describe treatment patterns (eg, treatment duration, incidence of dose interruptions, dose reductions, relative dose intensity, treatment sequencing), safety outcomes (eg, hepatotoxicities, SAEs, Grade 3 to 5 AEs, dose modifications and discontinuations due to AEs), and clinical outcomes (eg, OS) in patients with HCC treated with sorafenib.
- To describe the demographic and baseline disease-related characteristics of patients with advanced or unresectable HCC treated with lenvatinib or sorafenib, and their association with treatment choice and clinical safety outcomes.

1.5 Study Design

Study 508 was a prospective, non-interventional, open-label, multicentre, observational, Phase 4 study in patients with HCC treated according to approved local prescribing conditions of lenvatinib or sorafenib. Safety data (hepatotoxicity, SAEs, Grade 3 to 5 AEs, dose modifications and discontinuations due to AEs) were collected from the time of first prescription to 28 days after treatment discontinuation, or the end of the observation period (for patients with treatment ongoing). Each patient was followed for survival.

1.6 Setting

This final study report presents data from 44 sites in 10 countries (Australia, Austria, Germany, Italy, Portugal, Russia, Spain, Sweden, UK, US) representing a Western population.

1.7 Subjects and Study Size, Including Dropouts

In accordance with the PRAC recommendation at the time of the initial post-authorisation safety study, the target sample size was planned to be 500 lenvatinib and 500 sorafenib patients. As agreed with EMA, the study has been closed and this final report presents the analysis of data for 193 lenvatinib-treated patients and 123 sorafenib-treated patients enrolled at the time of the data cutoff date (27 Mar 2024). The inclusion of results from patients treated with sorafenib facilitates interpretation of the lenvatinib-exposed cohort results; however, no formal statistical comparisons between the data for lenvatinib-treated patients and sorafenib-treated patients were planned or conducted.

1.8 Variables and Data Sources

Data were collected on study eligibility, demographics and baseline disease characteristics, medical history, concomitant medications, liver function, prior anticancer treatments, treatment patterns, survival, and safety events of interest, including (but not limited to) hepatic toxicities and renal impairment.

Data were collected during visits that occurred within routine clinical practice. Historical data were sourced from medical records.

1.9 Results

The demographic and disease characteristics of the lenvatinib-treated patients and the sorafenib-treated patients were similar. For the 193 lenvatinib-treated patients and 123 sorafenib-treated patients, respectively, the median age was 69.0 years (for both), 31.6% and 28.5% were aged 75 years or older, most were White (82.4% and 87.8%), male (77.7% and 82.9%), and had an Eastern Cooperative Oncology Group performance status of 0 or 1 (74.6% and 76.4%). Baseline disease characteristics and concurrent conditions of clinical interest for lenvatinib-treated and sorafenib-treated patients, respectively, were: Child-Pugh A (58.0% and 56.1%), Child-Pugh B (14.5% and 17.1%), Barcelona Clinic Liver Cancer (BCLC) Stage B (27.5% and 22.8%), BCLC Stage C (27.5% and 26.8%), hepatitis C

(29.0% and 30.9%), and hepatitis B (13.0% and 12.2%), underlying cirrhosis (67.9% and 71.5%), and alcoholic liver disease (33.2% and 38.2%).

Primary Endpoint

This study met its primary objective, to characterise hepatotoxicity and the overall safety profile of lenvatinib in a real-world Western population of HCC patients treated with lenvatinib per the approved prescribing conditions.

Lenvatinib

Hepatotoxicity and the overall safety profile for lenvatinib in the Western population of patients in Study 508 were generally consistent with registrational HCC Study 304 and the approved product label.

Hepatotoxicity

- In the Hepatotoxicity category of treatment-emergent adverse events (TEAEs), 26.9% of patients experienced at least 1 TEAE; the most commonly reported (at least 5% of patients) were hepatic encephalopathy (15 patients, 7.8%), ascites (13 patients, 6.7%), and blood bilirubin increased (10 patients, 5.2%). Hepatic encephalopathy was reported as an SAE for 13 patients (6.7%); hepatic failure and hyperbilirubinemia were each reported as SAEs for 2 patients (1.0%). Treatment was discontinued due to hepatotoxicity TEAEs in 14 patients (7.3%). Hepatotoxicity TEAEs of Grade 3 or higher were reported for 22 patients (11.4%), of which 2 (1.0%) were fatal.

Overall Safety Profile

- 85.0% of patients experienced at least 1 TEAE, 45.1% had Grade 3 to 5 TEAEs, 38.3% had SAEs, 50.8% had TEAEs leading to treatment modification (treatment interruption or dose reduction), and 29.5% had TEAEs leading to lenvatinib discontinuation.
- TEAEs reported for 10% or more of patients were decreased appetite (28.5%), diarrhea (25.9%), fatigue (24.4%), hypothyroidism (15.5%), nausea (15.0%), weight decreased (14.5%), asthenia (12.4%), dysphonia and hypertension (11.9% each), and abdominal pain (10.9%).
- TEAEs leading to treatment modification in at least 5% of patients were diarrhea (13.0%), decreased appetite (7.8%), fatigue (5.7%), and nausea and vomiting (5.2% each).
- 29.5% of patients experienced at least 1 TEAE leading to treatment discontinuation; the most frequent were hepatic encephalopathy (4.7%), decreased appetite (3.1%), fatigue and nausea (2.6% each), and acute kidney injury, asthenia, and diarrhea (2.1% each). No other TEAEs leading to treatment discontinuation were reported for more than 3 patients.
- 38.3% of patients experienced at least 1 SAE; the most frequently reported were hepatic encephalopathy (6.7%), acute kidney injury (4.7%), cardio-respiratory arrest and general

physical health deterioration (2.6% each), and abdominal pain, diarrhea, and pneumonia (2.1% each).

- Fatal TEAEs were reported for 22 patients (11.4%). Cardio-respiratory arrest was reported for 5 patients (2.6%), and cardiac arrest and septic shock were each reported for 2 patients (1.0%); all other fatal TEAEs were reported for 1 patient. Three fatal TEAEs (duodenal perforation, hepatic encephalopathy, infection) were judged by the investigator as treatment related.

Sorafenib

- Overall, the safety profile of sorafenib was consistent with the safety profile observed in Study 304 and the approved product label.
- 84.6% of patients experienced at least 1 TEAE, 43.9% had TEAEs of Grade 3 or higher, 33.3% had hepatotoxicity TEAEs, 34.1% had SAEs, 43.1% had TEAEs leading to treatment modification, and 20.3% had TEAEs leading to sorafenib discontinuation.
- The most common TEAEs (≥10% of patients) were diarrhea (31.7%), decreased appetite (26.0%), fatigue and asthenia (21.1% each), nausea (13.0%), and ascites and palmar-plantar erythrodysaesthesia syndrome (11.4% each).
- 34.1% of patients experienced at least 1 SAE; the most frequently reported were hepatic encephalopathy (4.9%), hemorrhage (4.1%), anemia and ascites (3.3% each), and jaundice and renal impairment (2.4% each).
- Fatal TEAEs were reported for 4.9% of patients; no fatal TEAEs were reported for more than 1 patient, and none were judged by the investigator as treatment related.

1.10 Discussion

In a heterogeneous population of Western patients with HCC in the real-world setting, lenvatinib had a manageable safety profile that was overall consistent with the known safety profile of lenvatinib as established in the pivotal HCC Study 304; no new safety signals were identified. Adverse events were effectively managed by standard clinical practice and as applicable for treatment with lenvatinib. With regards to hepatotoxicity, no new findings were identified; the incidence and severity of hepatic-related toxicity were overall consistent with the known safety profile of lenvatinib in HCC, and events were effectively managed. The results of the final data analysis are overall consistent with the results of the interim data analysis, with minor differences which may be expected due to the increased number of patients and the longer duration of treatment and follow up. The overall safety profile of sorafenib (in any line of therapy) was consistent with that observed in Study 304 (in the first-line setting).

1.11 Marketing Authorisation Holder(s)

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1.12 Names and Affiliations of Principal Investigators

The study was conducted at 44 sites in the EU, UK, US, Russia, and Australia. A list of Principal Investigator names and affiliations is referred to in Annex 1.