STATISTICAL ANALYSIS PLAN (SAP)

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1. Study Populations and Model Setup for Analysis

Study Framework: This is a Phase 4 randomized, single-blinded interventional trial utilizing a **Parallel Assignment** model design involving **134 actual enrolled participants** allocated across **2 arms** in the clinical settings of Vietnam. The population consists of non-healthy patients aged 18–80 years. Patients presenting with unstable cancer or decompensated cirrhosis at baseline are excluded from analysis populations.

Intent-to-Treat (ITT) Population: Includes all 134 enrolled participants randomized into their respective arms who received at least one dose of their assigned intervention layout. This population serves as the primary dataset for comparative efficacy analyses.

Per-Protocol (PP) Population: Includes all randomized participants who completed the designated parallel follow-up period up to October 10, 2025, with strict adherence to their assigned drug maintenance schedule and without major protocol violations.

Safety Population: Includes all participants evaluated for adverse events over the 8-year longitudinal observation period from November 30, 2015, to April 20, 2026.

2. Endpoint Analyses

Primary Efficacy Endpoint Analyses:

1. Analysis of Liver Stiffness Measurement (LSM Success Rate): The success rate of transitioning from advanced cirrhosis (F3-F4) to lower stages (F2 or F1) will be compared between treatment arms at Year 1, Year 2, and Year 3 against Baseline measurements using mixed-effects repeated measures models (MMRM).

2. Analysis of HCC Development/Recurrence Incidence: The proportion of participants progressing to or developing HCC over time will be analyzed using Chi-square tests for landmark percentages and Kaplan-Meier curves with log-rank testing.

Secondary Efficacy Endpoint Analyses:

3. Analysis of Hepatic Synthetic Function (Albumin & INR Profiles): Continuous longitudinal values of serum Albumin (g/L) and INR collected at each 6-month tracking interval up to Year 3 will be analyzed using Linear Mixed-Effects Models (LMM) to determine inter-group divergence.

4. Continuous Evaluation of Liver Stiffness (kPa Trajectories): Continuous changes in liver stiffness measurements expressed in kilopascals (kPa) derived from ultrasound-based

transient elastography every 6 months up to 3 years will be analyzed utilizing Analysis of Covariance (ANCOVA) or Generalized Estimating Equations (GEE) to evaluate the speed and regression rate of liver cirrhosis between treatment arms, adjusting for Vietnamese sub-populations (such as HIV/HCV co-infections or stable cancer patients).

3. Role of the Data Monitoring Committee (DMC)

The independent Data Monitoring Committee (DMC) performed regular safety and efficacy data reviews throughout the active trial history (2015–2026) to ensure participant safety and trial scientific validity across the long-term follow-up window for the 134 enrolled patients.

4. Handling of Missing Data

Given the 8-year longitudinal nature of this Phase 4 trial and multi-year primary/secondary endpoints (6-month iterative tracking up to Year 3), missing clinical data points resulting from participant dropouts will be rigorously addressed. Primary analyses will apply Multiple Imputation (MI) techniques under the Missing at Random (MAR) assumption, with Last Observation Carried Forward (LOCF) utilized as a sensitivity analysis.

5. Statistical Software & Significance Level

All statistical tests are two-sided with a significance threshold set at $\alpha = 0.05$ ($p < 0.05$).

Analyses will be performed using standard statistical software packages (SPSS, SAS, or R).