Appendix A

REGENERATE: Design of a Pivotal, Randomised, Phase 3 Study Evaluating the Safety and Efficacy of Obeticholic Acid in Patients With Fibrosis Due to Nonalcoholic Steatohepatitis

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Table A.1: Interim Exploratory Objectives and Assessments

Month 18 Interim Analyses (All Patients)	
Exploratory Objectives	**Assessment**
Improvement in fibrosis (modified Ishak criteria)	A reduction in fibrosis stage from baseline of ≥1 based on liver biopsy using modified Ishak criteria
Improvement in SAF score	A reduction in the components of the SAF score and a reduction in total SAF score by ≥2 points
Markers of glucose metabolism	Fasting glucose, fasting insulin, C-peptide, HbA1c, HOMA-IR
Anthropometric measures	Weight, BMI, waist and hip circumference, waist-to-hip ratio
Markers of inflammation	hs-CRP
Markers of cardiovascular safety	LDL, HDL, VLDL, total cholesterol, triglycerides, blood pressure, CV risk scores (FRS, Reynolds score, SCORE)
Patient-reported outcomes	EQ-5D-5L, CLDQ-NAFLD, WPAI
Measures of apoptosis	CK-18-M30, CK-18-M65
Noninvasive scores of liver fibrosis	NFS, FIB-4, ELF, FibroTest/FibroSure, APRI, BARD
PD (bile acid precursor) of OCA	C4, FGF-19, bile acids
Adjudicated CV events for CV outcomes assessment	CV events including core MACE (CV death, non-fatal myocardial infarction, non-fatal stroke), expanded MACE (unstable angina requiring hospitalisation, transient ischaemic attack, peripheral or coronary revascularisation procedures, hospitalisation for congestive heart failure, and other cardiovascular events that include urgent outpatient visits for heart failure and arrhythmias)
Safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)

Month 18 Interim Analyses (Subset of Patients)	
Exploratory Objectives	**Assessment**
Morphometric assessment of quantitative collagen	PCA assessed by computerised reading of Sirius red-stained liver biopsy specimen
PK of OCA	OCA, tauro-OCA, glyco-OCA, total OCA, OCA glucuronide, potentially other conjugates or metabolites not yet identified
Noninvasive radiological liver fibrosis measurements	TE using the Fibroscan® TE device; MRE; ultrasound-based shear wave technologies other than TE, such as ARFI or multi-parametric MRI

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase -to-platelet ratio index; ARFI, acoustic radiation force impulse; BARD, BMI, aspartate aminotransferase-to-ALT ratio, diabetes; BMI, body mass index; C4, 7α-hydroxy-4-cholesten-3-one; CK-18, cytokeratin-18; CLDQ, Chronic Liver Disease Questionnaire; CV, cardiovascular; ECG, electrocardiogram; ELF, enhanced liver fibrosis; FGF-19, fibroblast growth factor 19; FIB-4, fibrosis-4; FRS, Framingham risk score; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment – insulin resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; OCA, obeticholic acid; PCA, percent collagen area; PD, pharmacodynamics; PK, pharmacokinetics; SAF, steatosis, activity, and fibrosis; SCORE, Systematic Coronary Risk Evaluation; TE, transient elastography; TEAE, treatment-emergent adverse event; VLDL, very low–density lipoprotein; WPAI, Work Productivity and Activity Index.

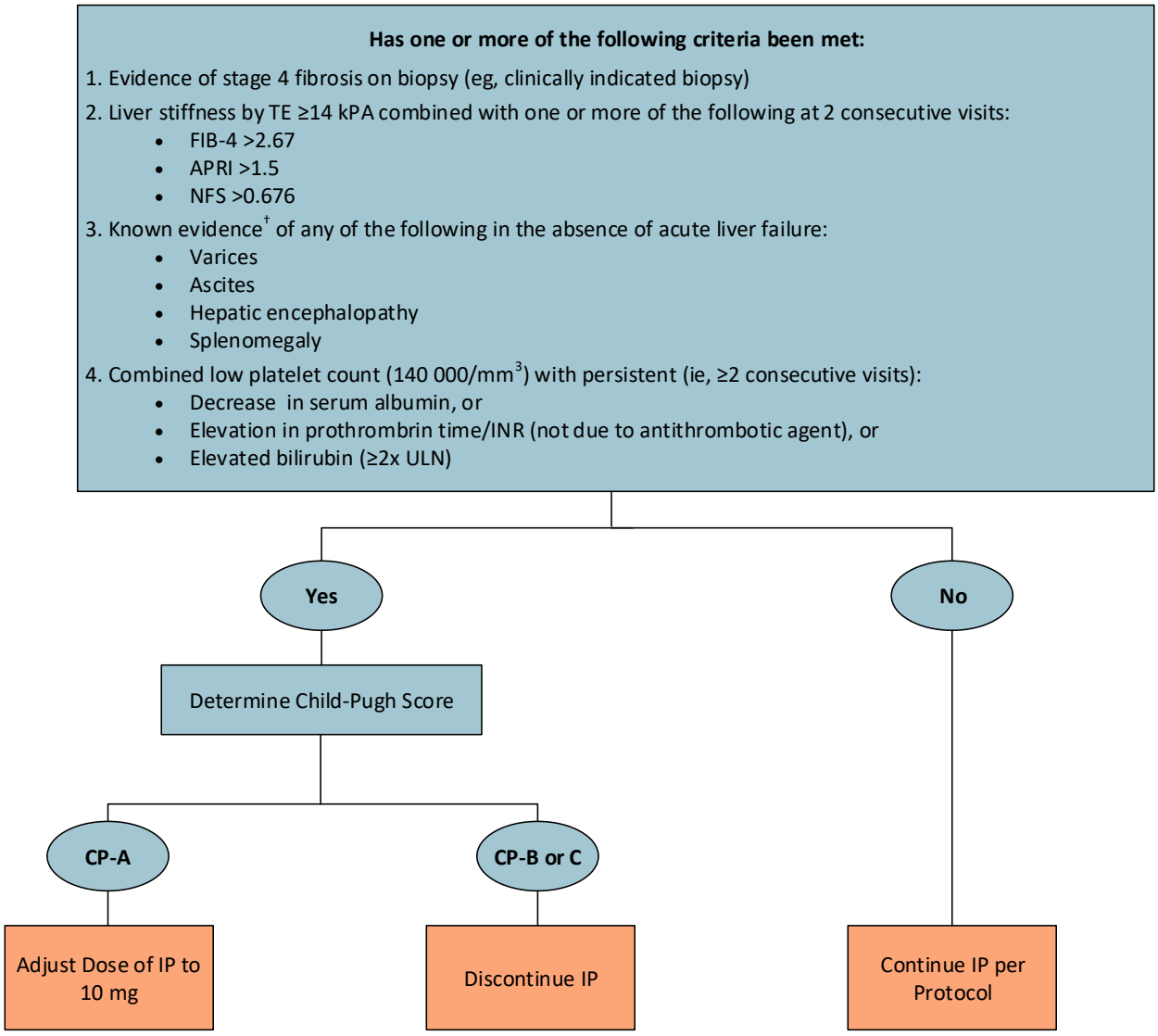
Table A.2: End-of-Study Exploratory Objectives and Assessments

End-of-Study Analyses (All Patients)	
Exploratory Objectives	**Assessment**
Individual components of the clinical outcomes composite endpoint and liver-related death	The following events: death (all cause); MELD score ≥15; liver transplantation; hospitalisation (as defined by a stay of ≥24 hours) for onset of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥2), or spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis); ascites secondary to cirrhosis and requiring medical intervention (e.g. diuretics or paracentesis) or histologic progression to cirrhosis
Hepatocellular carcinoma	Time to first occurrence (adjudicated)
Patient-reported outcomes	CLDQ-NAFLD, WPAI
Noninvasive scores of liver fibrosis	NFS, FIB-4, ELF, FibroTest/FibroSure, APRI, BARD
Adjudicated CV for CV outcomes assessment	CV events including core MACE (CV death, non-fatal myocardial infarction, non-fatal stroke), expanded MACE (unstable angina requiring hospitalisation, transient ischaemic attack, peripheral or coronary revascularisation procedures, hospitalisation for congestive heart failure, and other cardiovascular events that include urgent outpatient visits for heart failure and arrhythmias)
Long-term safety and tolerability	TEAEs, ECGs, vital signs, clinical laboratory assessments (including lipid profile changes)
Correlation between histology and noninvasive scores of liver fibrosis with clinical outcomes	Correlation between histology and noninvasive scores of liver fibrosis with the clinical outcome composite endpoint at the end of the study

End-of-Study Analyses (Subset of Patients)	
Exploratory Objective	**Assessment**
Noninvasive radiological liver fibrosis measurements	TE using the Fibroscan® TE device; MRE; ultrasound-based shear wave technologies other than TE, such as ARFI or multi-parametric MRI

Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse; BARD, body mass index, aspartate aminotransferase-to-alanine aminotransferase ratio, diabetes; CLDQ, Chronic Liver Disease Questionnaire; CV, cardiovascular; ECG, electrocardiogram; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; MACE, major adverse cardiovascular events; MELD, model of end stage liver disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; TE, transient elastography; TEAE, treatment-emergent adverse event; WPAI, Work Productivity and Activity Index.

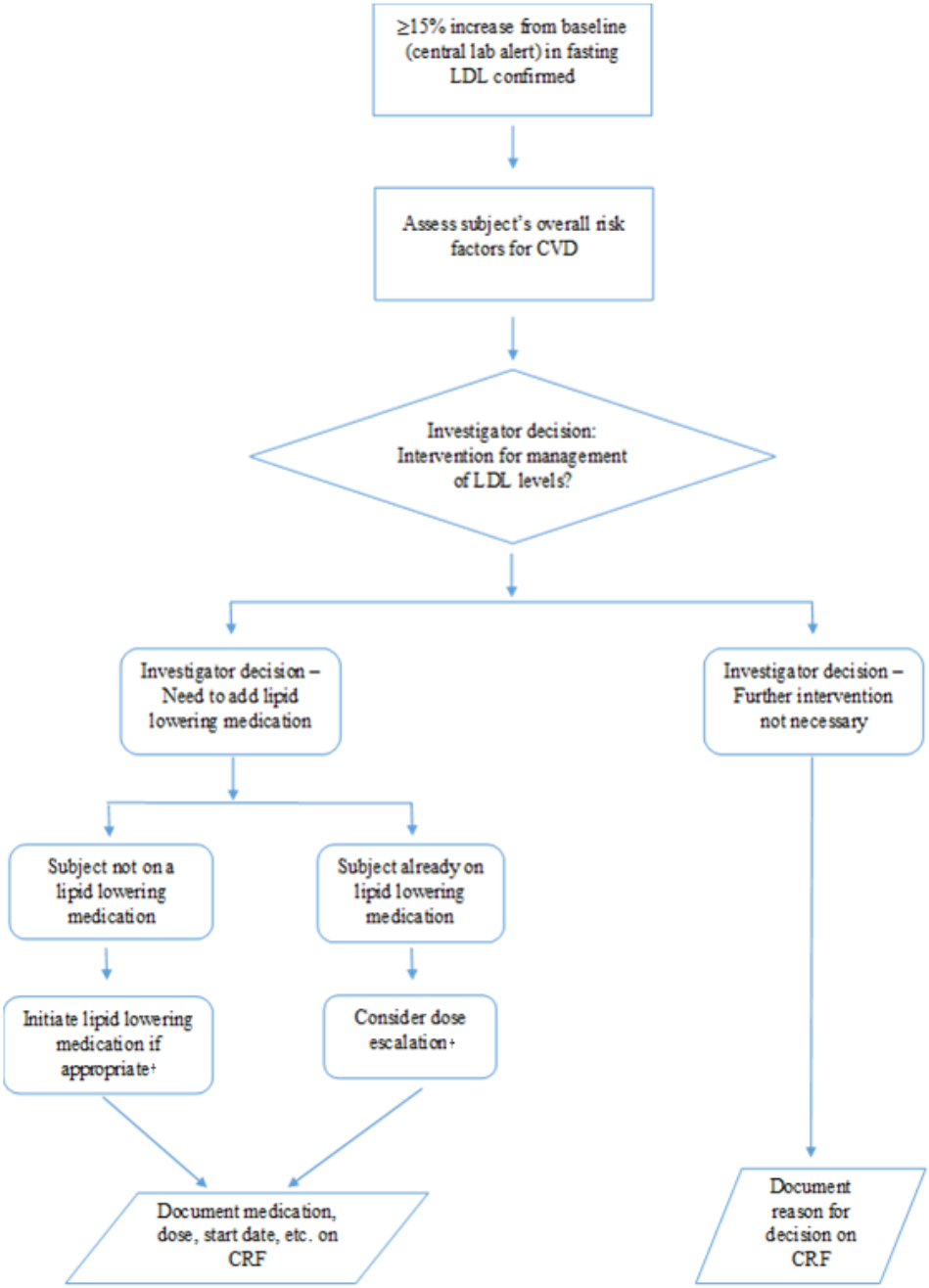
Fig. A.1: Algorithm for Determining Progression to Cirrhosis



Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; CP, Child-Pugh; EGD, esophagogastroduodenoscopy; FIB-4, fibrosis-4; INR, international normalized ratio; IP, investigational product; NFS, nonalcoholic fatty liver disease fibrosis score; TE, transient elastography; ULN, upper limit of normal.

†It is not necessary to rule out the occurrence of varices, ascites, hepatic encephalopathy, or splenomegaly at each visit; however, if at any time during the clinical management of the patient there are signs and symptoms suggestive of any of these events (e.g. ascites or splenomegaly noted on ultrasonography or varices noted on clinically indicated EGD), then the patient may be considered to meet criterion #3 for progression to cirrhosis, and a Child-Pugh screen must be assessed for that patient.

Fig. A.2: Low-Density Lipoprotein Management Flow Chart



Abbreviations: CRF, case report form; CVD, cardiovascular disease; LDL, low-density lipoprotein.

†If a patient is unable to tolerate statins, other lipid-lowering modalities may be considered and must be documented, including the reason for choice of medication.