Liver Forum
NASH Cirrhosis

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On behalf of the Working Group

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Ascites Definitions

Decompensating event	Case definition	Considerations and recommendations for clinical trials	"Grey zone"* and recommendations
Ascites	• Clinically overt based on physical examination • Free fluid in abdomen on imaging (ultrasound, CT, MRI, etc.)	• Prior to initiating NASH cirrhosis clinical trials, obtain a baseline ultrasound to assess the presence of ascites. Consider for decompensated trials, "treatment requirement" with diuretics that may strengthen the certainty of ascites and decompensation. • Could consider hepatic hydrothorax in the absence of ascites and after exclusion of other causes of pleural effusion as an "ascites equivalent"	• Perihepatic ascites only on imaging • Previous episode of transient ascites related to a precipitant (excess salt, VH, etc.) now resolved • We recommend excluding these patients from phase 2 trials. However, it might be beneficial to include a subpopulation of these patients in phase 3 studies. Such patients should be analyzed separately, and their enrollment should be designed with the regulatory authorities at the planning stages.

Variceal Hemorrhage (VH) Definitions

Decompensating event	Case definition	Considerations and recommendations for clinical trials	"Grey zone"* and recommendations

Variceal hemorrhage	• Upper GI hemorrhage that required hospitalization and on endoscopy showed any of the following:
	  ○ Varix spurting blood
	  ○ Varix with overlying clot or white nipple
	  ○ Only varices and no other lesion
		• Acute (not chronic) bleeding from portal hypertensive gastropathy that required hospitalization may be considered a "VH equivalent"
		• We recommend waiting for a period of 3 months or more for stability prior to enrollment in NASH decompensated clinical trials.
			• Previous (>1-2 years) episode of documented VH that required hospitalization and has not developed re-bleeding (could still be on a stable dose of NSBB)
			• Chronic bleeding from portal hypertensive gastropathy
			• We recommend inclusion of a subpopulation of TIPS in phase 3 trials might be an option upon discussion with the regulatory authorities, and depends on the outcome of the trial, mechanism of drug action and duration since the TIPS.

Hepatic Encephalopathy (HE) Definitions

Decompensating event	Case definition	Considerations and recommendations for clinical trials	"Grey zone"* and recommendations
HE	• Overt (≥ grade 2) HE per the AASLD/EASL guidelines	• Consider "requiring treatment" as evidence of chronic decompensation • Consider "requiring hospitalization" as stronger evidence of definitive HE • We recommend that the investigator performs a thorough chart review to investigate the initial diagnosis, although this is often missed and is essential for the diagnosis.	• Previous transient episode of overt HE related to a precipitant (infection, VH, metabolic, etc.) now resolved, not requiring treatment • Covert (minimal or grade 1) HE (no prior history of overt HE) currently on treatment. May be excluded from phase 2 studies and limited in phase 3 • HE occurring primarily due to porto-systemic cause (e.g. occluded shunt)

*Specific trials may include or exclude patients fulfilling grey zone criteria from compensated trials but these patients should be analyzed as a separate subgroup analyses or stratified at randomization, especially if they are a large component of the total population.

Decompensated Cirrhosis: Stratification for Clinical Trials (Work-in-Progress)

	Early decompensation	Advanced Decompensation
Population	- Patients^ with a history or presence of single decompensating event (ascites, variceal bleed, or encephalopathy) but well controlled on specific therapy - Consider (or not) patients in grey zone	- Patients^ with history or presence of two or more decompensating events (ascites, variceal bleed, encephalopathy)
Stratification	- Grey zone or not - CP A vs early B - Type of decompensation event – ie, ascites vs other - Other co-morbidities (CKD, CHF, coronary artery disease, etc) - MELD (lower vs. higher)	- Gray zone or not - CP B vs CP C - Other co-morbidities (CKD, CHF, coronary artery disease, etc) - MELD (lower vs. higher) - Presence/ absence of ascites
Primary endpoint	- Second decompensating event, further decompensation, or death	- Death

	Early decompensation	Advanced Decompensation
Primary endpoint	- Second decompensating event, further decompensation, or death	- Death
Outcomes	**Clinical (primary)** - Development of a 2nd type of decompensation event - Further decompensation (refractory ascites or refractory HE, SBP, HRS) - Critical illness requiring hospitalization - Death (all-cause mortality) -Re-compensation? **Surrogate (candidate):** – Progression in MELD* **Exploratory:** - improvement in functional test - additional emerging biomarkers **Safety:** - HCC**	**Clinical (primary):** - Death (all-cause mortality) **Clinical (secondary):** - Further decompensation (refractory ascites or refractory HE, SBP, HRS) - Critical illness requiring hospitalization **Surrogate (candidate):** - Progression in MELD* **Safety:** - HCC**

^ patients with hepatopulmonary syndrome or portopulmonary hypertension would likely be excluded from these trials

* MELD – general term for MELD and MELD sodium

** HCC not outcome but confounding variable – consider as competing event unless trial specifically for HCC

Transplant would not be an outcome but would be treated as a competing event